PB31

RESPIRATORY CANCER

Collected Scientific Excerpts
1961

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RESPIRATORY CANCER

Collected Excerpts from Scientific Literature

This reference work is comprised of excerpts from published literature concerning medical and scientific research on problems of respiratory cancer. It has been prepared from the scientific library of the Tobacco Industry Research Committee and is made available in this form as an information paper.

1961

Compiled by: Tobacco Industry Research Committee, 150 East 42nd Street, New York 17, N.Y.

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INTRODUCTION

This collection of excerpts presents the results of research by many scientists into the causes, nature, and incidence of human respiratory cancer. Most of the authorities quoted have made cancer research their life work. In assembling these representative selections from a vast scientific literature, it is expected that the data from various disciplines and areas of investigation will prove of interest and value to workers in these scientific fields. Among the scientific disciplines represented here are surgeons, pathologists, internists; cytologists, roentgenologists and other medical specialists; biochemists and other laboratory researchers, and biostatisticians.

Few practicing physicians and scientists find time to personally research the literature, or to assemble and read the growing volume of documentation on respiratory cancer. Accordingly, these excerpts have been kept as brief as possible and yet remain faithful to the authors' views on the points presented. They can serve as a guide to the context of the full papers.

It will be clear to the reader that these scientists do not consider that there is any simple answer or any single answer to the problem of respiratory cancer. The fact that conscientious workers do not agree in their conclusions shows that research has not been limited to a narrow, one-way track. Perhaps the more important differences are on such questions as these:

- Is respiratory cancer really increasing by leaps and bounds, or is it only recognized oftener than in the past?

- Can respiratory cancer be caused by inhaled solid, liquid, and gaseous substances or by viruses, hormonal disturbances, and previous respiratory diseases?

- Do inherited characteristics or the many stressful aspects of modern civilization play dominant or contributory roles in the onset of cancer?

- Do combinations of such varied possible factors determine the onset of cancer and its specific localization in the body?

One of the hopeful signs for the future is the fact that present and projected research is not limited to any one of the possible causes of respiratory cancer. Many authors have noted that their results have raised more questions than they have answered. The recent results of research have emphasized the great complexities of respiratory cancer. Hence, it is imperative that encouragement and support be given to continued and expanded research along every path that may lead to a solution of the problem. Perhaps scientists will find a way to cure cancer before they have determined its cause or causes.

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This survey recognizes the claims by those who believe that respiratory cancer is due primarily to the action of inhaled substances, particularly cigarette smoke, on the lungs. Such claims have been reiterated with emphasis during the past six years. Numerous scientists in many countries have investigated this theory. However, no qualitatively new data regarding the question of tobacco's effect have been produced since the original reports. On the other hand, a good deal more evidence has appeared that points in quite other directions.

Further, scientists are not all preoccupied with this single "tobacco" approach to respiratory cancer: of 295 papers presented at the American Association of Cancer Research proceedings in April 1960, only three were concerned with tobacco. There were eight papers on tobacco and nicotine among 2526 papers presented before the Federation of American Societies for Experimental Biology, also in April 1960. Similar relationships of tobacco research to general research in cancer and other human diseases are shown in the proceedings of both these organizations in 1959, 1958, 1957 and prior years.

It seems likely that an emotional response has been awakened by the disproportionate attention given to the tobacco-lung cancer theory in lay publications and on occasion in medical journals. Much of the research on tobacco has been most valuable and is an important contribution to our knowledge. It should be continued. Until research has discovered the cause or causes of respiratory cancer every possible lead must be followed diligently, with appropriate scientific detachment, so that the truth may be known.

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I. WHAT CAUSES LUNG CANCER?

Few biological problems have proved more difficult--and more fundamental--than the question of cancer's cause or causes. More than half a century of medical research has yielded knowledge of a relative handful of specific carcinogens, but not any widely applicable principles of cancer causation or any real understanding of the mechanisms involved.

The continuing search spans all the disciplines of medicine and biology. Hundreds of scientific papers on carcinogenesis are published in medical journals in every country every month--thousands every year. The conflicting evidence and opinions in this massive outpouring of work attest both to the uncertainty of our knowledge and the need for further studies, for each new fact raises at least as many questions as it answers.

What is true of cancer in general is, of course, true of the question of respiratory cancer and the various other forms of intrathoracic tumors in humans. No one yet has adequate answers; no single theory fits all the facts. The highly publicized studies of tobacco use and lung cancer will be discussed further along in this survey. It is the purpose of this section to report the reasonings and conclusions of leading authorities, who, with many others, have firm opinions on what may cause lung cancer.

These opinions fall into four general groupings. They hold that:

A. Lung cancer is related to numerous and varied factors.

B. Lung cancer is related to previous respiratory disease.

C. Lung cancer is related to occupational and environmental causes.

D. Lung cancer is related to stress, viruses, hormonal disturbances and genetic factors.

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A. LUNG CANCER IS RELATED TO NUMEROUS AND VARIED FACTORS

Many authors have reviewed the extensive literature on lung cancer and have listed the various external and internal factors suspected of causing the disease. The following selections are typical of the opinions expressed.

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CLEARLY IDENTIFIED LUNG CANCER AGENTS LISTED

G. Burroughs MIDER, M.D., Associate Director of the National Cancer Institute in Charge of Research, reported his findings in September 1956 (29-m) as follows:

> "The total effort of all interested parties has produced, over the years, only six clearly identifiable agents that are known to cause cancer in man: (1) x-rays and some of their constituent parts (whether generated by machines or by artificially induced or naturally occurring radioactive substances makes little difference if experimental data are correct), (2) ultraviolet irradiations, (3) arsenic, (as potassium arsenite, usually after prolonged medication), (4) beta-naphthylamine, (5) benzidine, (6) 4-aminodiphenyl.....
>
> "A much larger number of substances, essentially mixtures, has been incriminated in the production of cancer in man. Soots, shale oils, paraffins, undefined materials associated with the production of nickel, chromates, and isopropanol have increased the hazard of developing one or more types of cancer among persons exposed.
>
> "The list is not complete, but interest in the others is far overshadowed by a suspected etiologic relationship between certain environmental factors and the increasing frequency of pulmonary cancer."

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MANY THINGS BLAMED FOR LUNG CANCER

R. H. RIGDON, M.D., Professor of Pathology at the University of Texas Medical Branch, Galveston, listed some of the various factors which have been blamed for lung cancer (10-r) as follows:

> "Time does not permit a discussion of the many agents which have been suggested as the etiology of lung cancer. Among those considered have been tuberculosis (11-e), syphilis (18-p), influenza (11-b), diphtheria and measles (25-m), chronic pulmonary inflammation (19-d), pulmonary scarring (23-w), road dust (2-w), dust from grooming horses (31-h), motor exhaust (39-m), war gas (36-b), cigar makers and sorters (34-b), arsenic (4-n), chromium (1-u), asbestosis (26-l), silicosis (5-f), metaplasia (1-k), tar (25-p), heredity (12-s), trauma (10-w), air pollution (32-m), cigarette smoking (27-w), and inhalation of printers ink while reading the morning newspaper (9-a)."

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VIRUSES
AND CANCER

Chester M. SOUTHAM, M.D., Head of the Oncogenic Virology Section of the Sloan-Kettering Institute, discussed viruses in the field of cancer in a recent symposoum on cancer (31-s):

> "Cancer is very frequently discussed as if it must be the result of a single type of causative agent. Such an exclusive concept seems entirely unjustified. To espouse the hypothesis of viral oncogenesis does not necessitate the abandonment of unquestionable evidence that chemicals, radioactivity, hormones, and genetics are causative factors in these diseases.
>
> "On the contrary, the experimental data lend credence to the idea that neoplastic diseases are often, perhaps usually, a result of coincidence of multiple forces rather than of a single etiologic factor....
>
> "Thus, the apparent barriers to acceptance of viruses as possible oncogenic agents in man have disappeared under the gradual accumulation of experimental evidence. There still remains unanswered, however, the ultimate objection that, as yet, there has been no direct evidence that any human cancer is in fact of viral etiology."

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NO ONE AGENT EXPLAINS LUNG CANCER

Paul E. STEINER, M.D., Professor of Pathology at the University of Chicago, in 1954 analyzed "Etiologic factors in cancer revealed by ethnic and geographic studies" (37-s) as follows:

> "The cause of human lung cancer cannot be explained by a single agent any more than is pneumonia which has numerous bacterial, viral, parisitic, and chemical causes among which a few agents predominate and account for most of the cases. In pneumonia, the predominating agent may vary with geography, race, time, and other factors. So it appears to be in lung cancer. No one agent accounts for all cases. The tumors that are found in Himalayan tigers and other animals, in infants and children, and in non-smoking adults cannot be attributed to cigarette smoking....
>
> "The sex difference in frequency of those tumors which are not sex-limited probably, at least in part, indicate unequal exposure to some environmental agent.... In the Mexicans of Los Angeles, the virtual sex equalization of lung cancer at the high level usually shown by men is in contrast with the situation shown until recently in Norway where the sex difference was slight because of low levels in the males."

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For further reading on the conjectured origins of respiratory cancer see 3-a, 56-b, 57-b, 40-b, 54-h, 13-m, 14-m, 6-o, 52-p, 53-p, 54-p, 21-s, 35-s, 36-s, 38-s, 40-s

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B. LUNG CANCER IS RELATED TO PREVIOUS RESPIRATORY DISEASE

In the epidemiological detective work that must be done to understand lung cancer, researchers have found some of their best clues in the pattern of other respiratory diseases. As the toll of these afflictions--particularly tuberculosis and influenza--has dropped over the past several decades, the apparent incidence of more specific diagnoses such as lung cancer has increased.

Evidence that this may be more than a chance association comes first from studies of leading pathologists on both sides of the Atlantic at the time of the great influenza pandemic of 1917-19. At that time, many researchers who examined the lungs of influenza victims found multiple lesions which they considered to be pre-cancerous. On the basis of these findings, they predicted that many of those who survived might develop lung cancer in the years ahead.

Other pathologists found scars left on the lungs by healed or dormant tuberculosis, by chronic bronchitis and other lung diseases. Still others found lung cancers growing in the scar tissue. They, too, came to the conclusion that lung cancer might be an aftermath of earlier pathology of the respiratory tract.

Similar lesions have now been found in the lungs of victims of the Asiatic influenza pandemic of 1957.

Both clinical and statistical studies have confirmed this association between previous lung disease and lung cancer. Its significance--like that of all other statistical associations in the lung cancer picture--is still to be determined; but the following excerpts from the extensive literature on this aspect of the problem suggest its importance as a factor.

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Part 1 - The Older Literature

The toll of deaths in the United States during the influenza epidemic of 1918 awakened widespread interest among numerous pathologists who had studied the lungs of many of the victims and believed that many of the survivors had sustained lung damage that might lie dormant for years. The following selections are typical of such findings.

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METAPLASIA FROM INFLUENZA CAN BE CAUSE OF LUNG CANCER

Professor M. ASKANAZY, M.D., of the Institute of Pathology at Geneva, Switzerland, conducted autopsies on 320 victims of the influenza epidemic between July 11 and Dec. 31, 1918, and selected 90 tracheobronchial trees at random for microscopic study. He reported the formation of squamous epithelium in 38 cases (8-a), and said:

> "The transformation of the entire epithelium into squamous epithelium can be regarded as an act of regeneration or as the result of a direct formative irritation, as is the case with any inflammatory tissue proliferation.... The development of squamous epithelium in the air passages is not a specific factor in influenza, even in acute infections of the respiratory tract, for I recently noted it twice in genuinely typical pneumonia too.....
>
> "In connection with the development of tumors and metaplasia of the epithelium in the air passages, there has been... a concurrence of opinion to the effect that the squamous epithelium which forms the tumors is not embryonically aberrant but is produced metaplastically.... The fact that metaplasia can be a precancerous phenomenon remains undisputed."

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TUBERCULOSIS, INFLUENZA, SEEN LUNG CANCER FACTORS

Moses BARRON, M.D., of the Department of Pathology and Medicine, University of Minnesota Medical School, discussed the incidence, pathology and relative importance of carcinoma of the lung in 1922 (9-b), as follows:

> "A careful review of the literature demonstrates the increasing importance of this disease. Some of the reports are not reliable because cases are reported as primary carcinoma without necropsy or histologic studies. Statistical study, therefore, loses in value on account of the unverified cases....
>
> "Perhaps the chief etiologic factors are inflammatory conditions, and of these, tuberculosis is the most important.... Many series of cases in the literature have proved that carcinoma is not infrequently found associated with tuberculosis, developing especially in the scars and walls of tuberculous cavities....
>
> "I believe that it is not at all unlikely that another chronic inflammatory process may be responsible for a number of pulmonary cancers encountered during the past few years. It is possible that this might explain the rather striking increase in incidence recently. I have in mind the influenza epidemic of 1918-1919... In discussing this subject with pathologists from other hospitals I found that the same impression of an increase in incidence since 1918 seems to obtain."

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LUNG CANCER PREDICTED IN SURVIVORS OF INFLUENZA

Milton Charles WINTERNITZ, M.D., late Head of the Department of Pathology at Yale University, considered the lesions caused in lungs by the influenza epidemic of 1918, in a book written by him and his medical colleagues (21-w). They said:

> "It has seemed desirable to contribute to the pathology of various phases of influenzal pneumonia and to attempt to correlate this with other types of acute respiratory inflammation, in the hope that the prognostications which suggest themselves may be of aid in the prophylaxis and possibly in the treatment of the more insiduous and progressive pulmonary changes that may follow this disease...
>
> "It is rare to see such activity on the part of the epithelium as that frequently encountered in influenza. The alveoli may be lined by newly formed cubical cells, and mitotic figures in the injured bronchiolar lining occur in abundance.... In a number of cases, epithelial proliferation has been so extensive that it could not be differentiated histologically from an invasive, malignant neoplasm.
>
> "There is no reason to believe that malignancy might not result from the continuous stimulation of the epithelium to proliferate, in the chronic inflammatory process of the lung in influenza, just as chronic infection in the lung of a mouse results in a much higher percentage of spontaneous neoplasms of the respiratory tract in this species than in those animals where chronic pulmonary processes are uncommon. It will be interesting, indeed, to see whether, as a late manifestation, there is an increase in the number of now relatively rare epithelial new growths in the respiratory tract of man.
>
> "A basis for the interpretation of the respiratory lesions of influenza is offered by the analogous changes in the respiratory tract initiated by the inhalation of poison gases."

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ROLE OF CHRONIC INFLAMMATION IN LUNG CANCER

Michael G. WOHL, M.D., Pathologist at the Methodist Hospital of Omaha in 1920 when he wrote on lung cancer (22-w), is now at Philadelphia. In his paper he called attention to the relative neglect of lung cancer in those days:

> "The interest in primary tumors of the lungs has been renewed for two reasons -- first, due to the recent development of intrathoracic surgery and modern deep X radiation, the scientific diagnosis and therapy of the latter is becoming a matter of more than academic interest; secondly, the recent wave of pulmonary infections, such as streptococcic bronchopneumonia and influenza, constitutes an important factor in the formation of pulmonary neoplasia....
>
> "It must be stated that in the advanced form it is pretty nigh impossible to trace definitely the origin of these tumors, since the infiltrating tumor mass involves both bronchi and alveolar tissue. Histologically one may also find structures within a single tumor resembling the generally accepted cases of all three varieties....
>
> "That chronic inflammatory changes often precede or predispose to the formation of carcinoma is too well known to require detailed discussion.... Bayle, Wolf and others (quoted by Moise, 1921, p. 745) (10-b, 35-m, 23-w) have called attention to the frequent coexistence of carcinoma and tuberculosis of the lungs. In chronic bronchitis and in reparative lesions following bronchopneumonia there is often a marked epithelial overgrowth with frequent metaplasia of alveolar epithelium....
>
> "Thus there is considerable evidence in favor of chronic irritation preceding carcinoma. The possibility of carcinoma being induced by acute inflammatory changes has recently been brought to the medical attention by the work of Winternitz and his associates (1920) (21-w)."

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I-B 5* For other papers relating to observation of an association of respiratory lesions with bronchial carcinoma see 54-b, 10-b, 11-b, 11-e, 15-f, 26-g, 21-g, 30-h, 42-h, 51-m, 25-m, 48-m, 15-p, 34-p, 13-s, 22-s, 51-s, 48-s, 49-s, 23-w

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Part 2 -- The Recent Literature

There is a steadily increasing amount of modern research that shows lung cancer associated with prior or concurrent tuberculosis, pneumonia, influenza and lung lesions of diverse characters. A few typical quotations follow, and a supplemental bibliography is provided at the end of this section.

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LUNG CANCER ARISES IN HEMORRHAGIC SCARS IN LUNGS

Josef BALÓ, M.D., Eugen JUHÁSZ, M.D., and Judith TEMES, M.D. of the Department of Pathological Anatomy and Experimental Cancer Research, Medical University, Budapest, Hungary, have found the scars from internal bleeding associated with lung cancer development in fifty cases (3-b), and report similar findings by others in a 1956 paper. They said:

> "In the human lung, proliferation of alveolar epithelium frequently occurs in the border of hemorrhagic infarcts. Such epithelial proliferation may arise in several foci in the same infarct and can occur around several infarcts....
>
> "Lung cancer can develop from the epithelial proliferation at the site of infarcts. This can be alveolar-cell carcinoma, but through metaplasia squamous-cell carcinoma can also occur.
>
> "Epithelial proliferation occurring on the border of hemorrhagic infarcts of the lung cannot be the result of exogenous noxious agents but is the result of the action of endogenous factors. Anoxemia, regeneration, and the effect of irritative substances liberated at the site of necrosis -- necrohormones -- are responsible for this epithelial proliferation."

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LUNG CANCER IN WAR GAS SURVIVORS

R. A. M. CASE, of the Institute of Cancer Research, Royal Cancer Hospital, and A. J. LEA, of the British Ministry of Pensions and National Insurance, in 1955 wrote on "Mustard gas poisoning, chronic bronchitis and lung cancer (4-c)." They said:

> "We have made an examination of the mortality experience of 1,267 war pensioners who suffered from mustard gas poisoning in the 1914-18 war, and who were still alive on January 1, 1930. It was found that almost all (over 80%) had chronic bronchitis at that date. In subsequent years a statistically significant excess of deaths attributed to cancer of the lung and pleura has been observed amongst them (29 deaths found compared with fourteen expected).....
>
> "The evidence indicates that chronic bronchitis may be associated with the subsequent development of cancer of the lung and pleura, unless it is assumed that the excess of deaths attributed to this disease is entirely due to diagnostic bias."

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METAPLASIA IN LUNGS FROM 1957 INFLUENZA

Dr. P. DeBAAN of the Pathology Laboratory of Leiden State University, the Netherlands, reported in 1959 (4-d) that the metaplastic changes in the trachea and bronchi which were described in 1918 (see 8-a, 21-w) have been found in proven cases of influenza-virus infection in the 1957 epidemic too. He says:

> "Dutch investigators have shown that these epithelial changes arise after degeneration and sloughing off of the epithelium have already taken place, very early in the course of the illness.... The late epithelial changes therefore can be looked on as the result of regenerative growth.... They introduce the pathologic process and are still encountered long after the acute infection is over....
>
> "It is therefore possible that the 'tumorlets,' to the extent that they are of bronchiolar epithelial origin, originate in proliferation produced by a virus infection of the lung."

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PREVIOUS LUNG DISEASES FOUND ASSOCIATED WITH LUNG CANCER

A recent writer on this subject is Walter FINKE, M.D., of the Department of Medicine of the Genesee Hospital, at Rochester, N.Y., (8-f) who said:

> "The case histories of 86 patients with lung cancer were reinvestigated thoroughly in regard to previous chronic pulmonary diseases and severe respiratory illnesses. In addition, a roentgenologic history was obtained on 63 of these patients.
>
> "Sixty-five per cent of this group proved to have had a long-standing chronic bronchitis, often associated with chronic asthma or suspected to be tuberculosis. In six patients chronic pulmonary tuberculosis had been known to exist ten or more years before the discovery of the cancer. One had silicosis, and two a chronic chest ailment caused by gas poisoning in World War I.
>
> "The most frequent acute pulmonary illnesses in the patients' distant past were epidemic influenza in 1918-1920 and noninfluenzal pneumonia. Seventy-seven per cent had suffered at least one and 43% both of these illnesses or multiple attacks of pneumonia."

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LUNG CANCER PRECEDED BY TUBERCULOSIS

E. C. MEYER, M.D., J. H. SCATLIFF, M.D., and G. E. LINDSKOG, M.D., of the Departments of Surgery and Radiology, Yale University School of Medicine, in 1959 reported on their study of a possible connection between respiratory tuberculosis and bronchogenic carcinoma (28-m).

They said:

> "One hundred consecutive case histories of bronchogenic carcinoma were reviewed in which the tuberculin skin tests had been reported on the clinical record. Included in the data collected for each patient were the age, sex, smoking habits, past history of tuberculous contact or infection, and the histologic type of carcinoma and its operability.... Tuberculin skin tests...(also) were given to one hundred males in the same general age groups as those with bronchogenic carcinoma....
>
> "Ninety-five per cent of the carcinoma group had positive tuberculin reactions as opposed to 80 per cent of the control. There was a greater correlation between bronchogenic carcinoma and the positive tuberculin reaction than with cigarette smoking. Eighty-six per cent of the carcinoma group and 77 per cent of the control group were smokers....
>
> "Primary tuberculous foci were seen radiologically in 47 per cent of the (test) series.... In 15 of the 100 cases there was definite radiologic evidence of re-infection tuberculosis..... In only 10 of the 100 cases could an anatomic-radiologic association of tumor and tuberculous lesion be established....
>
> "Thirty-eight cases in the 100 comprising the carcinoma-tuberculin test group were subjected to the removal of a lobe or lung. Of these, 33 specimens were still available for study..... The pathologic reexamination of these 33 specimens...(added) four cases of pathologically associated tuberculosis and carcinoma to the 10 diagnosed radiologically....

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"One may conclude from these results that the tuberculin skin test, in cases of bronchogenic carcinoma, is more constantly positive than is the history of cigarette smoking....

"It seems reasonable to consider bronchogenic carcinoma as an abnormal process of epithelial regeneration in the lung. As with simple inflammation, it may have a variety of etiologic agents. Recent studies of 'lung-scar cancers' seem to support the theory that it is the scar, and only remotely the agent causing the scar, that is important in the pathogenesis of the disease.

"Tuberculosis is a common cause of pulmonary scars.... The shortcomings of a purely statistical approach to tumor pathogenesis is well demonstrated."

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ORIGIN OF LUNG CANCER IN SCARS FROM TUBERCULOSIS

Dr. Philip SCHWARTZ, Director of the Warren (Pa.) State Hospital, has been an authority on respiratory pathology for more than 40 years. In 1919 he was on the Medical Faculty of the University of Budapest, Hungary; later he was Professor of Pathology at the University of Frankfort, Germany, and for many years he was Chief of the Department of Pathology at the University of Istanbul, Turkey. Following are excerpts from a series of papers published in 1960 (65-s) on the origin of lung cancer in tuberculosis lesions:

> "Patho-anatomical and statistical investigations disclosed 1) that benign and malignant tumors often arise in bronchial scars of tubercular origin, and 2) that the spectacular increase in the frequency of malignant pulmonary tumors during the last decades in the United States was primarily caused by the transformation of the age-class composition of the population and the decrease in the tuberculosis mortality, which accompany growing prosperity....
>
> "In the morphological part of our program we evaluated not only observations in which benign and malignant tumors were associated with bronchial lesions of tubercular origin, but also numerous cases of common perforative scars....
>
> "Fresh lymphonodogenic lesions of the bronchial wall -- penetration and perforation foci -- occur both in primary infections and during the development of chronic pulmonary tuberculosis. We deal in these cases with the ingression of tuberculosis inflammation into the bronchi starting in recently diseased lymph nodes; the process displays all stages of an infiltration from the period in which the basic structure of the bronchial wall still is preserved, up to the complete destruction of cartilage and mucosa.

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"There are acute lesions which completely sever the continuity of the affected bronchus: we are speaking of mutilation defects. However, much more frequent are involvements which only cause circumscribed disruptions, erosions and ulcers, mostly of the anterior bronchial wall, and which eventually cicatrize without detaching the bronchial tube. Perforative foci of this group may sometimes appear very extensive -- we observed defects up to 4 cm. long and 3 cm. wide -- producing correspondingly large scars, funnel-shaped, flat, star-like, and sometimes resembling a surgical suture or a centipede.

"Nevertheless, in respect to the development of tumors, perforative lesions of a lesser size, producing small, flat or nodular, sometimes trough-shaped scars, are also important and, because of their frequency, perhaps even more so....

"Every person living in countries in which pulmonary cancer frequently occurs may be considered contaminated by tuberculosis up to the age of 30 at the latest. Thus, we may assume that lymphonodogenic bronchial lesions occur in practically every patient affected by bronchial cancer....

"According to observations made by the present author in Turkey, the United States and in Germany, clearly visible perforative scars occur in approximately 25% of the cases examined by routine autopsy in a general hospital.... No doubt, the actual number of perforative bronchial scars and their macroscopically invisible sequelae is much higher than can be discovered by bronchoscopy and autopsy."

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Similar views were expressed by Dr. C. Eugene WOODRUFF and associates, of the Detroit Department of Public Health, in 1952 (25-w):

> "The decrease in the death rate from pulmonary tuberculosis has been accompanied by a present-day increase in the number of persons in the 50- to 60-year group with healed primary tuberculosis foci.... It would seem from the present study, as well as from the work of others (6-s, 24-w), that in many cases the various pulmonary abnormalities left by the healing of a primary tuberculosis focus are factors of importance in the localization of bronchogenic carcinoma..... It seems evident that the young men who... were able to survive their primary tuberculosis infection are now, 30 to 40 years later, the persons particularly susceptible to the development of carcinomas of the lung."

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For other papers on the association of previous lung diseases and injuries with cancer see 67-b, 3-b, 9-b, 11-b, 12-b, 25-b, 60-b, 43-b, 49-b, 33-c, 36-c, 5-c, 6-c, 7-c, 8-c, 31-c, 21-c, 1-d, 25-d, 16-f, 1-g, 5-g, 32-g, 22-g, 17-h, 9-j, 5-l, 6-l, 25-l, 18-m, 61-m, 20-m, 27-m, 28-m, 31-m, 5-o, 6-o, 3-p, 46-p, 35-p 7-p, 8-p, 9-p, 48-p, 36-p, 1-r, 2-r, 3-r, 4-r, 5-r, 16-r, 70-s, 1-s, 6-s, 7-s, 9-s, 11-s, 10-s, 12-s, 15-s, 66-s, 27-s, 39-s, 2-t, 3-t, 9-t, 12-w, 14-w, 24-w

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C. LUNG CANCER IS RELATED TO OCCUPATIONAL AND ENVIRONMENTAL CAUSES

There is evidence that a variety of factors in human environments and occupations may play a role in specific cases of lung cancer, but there are differences of opinion on the extent and nature of their contribution to the total lung cancer incidence.

The finding of high lung cancer mortality in thickly-settled and industrial areas and the low death rates in rural areas is one illustration of this. Further comments on such factors are in Section II following.

Following are typical references on occupational and environmental factors believed related to lung cancer mortality.

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OCCUPATIONAL LUNG CANCER

Dr. P. Lesley BIDSTRUP, formerly of the Department of Research in Industrial Medicine at the London Hospital, England, discussed occupational causes of lung cancer in 1959 (18-b) as follows:

> "The occurrence of lung cancer as an occupational disease in certain industries has resulted in a tendency to claim that inorganic substances such as nickel, chromium and asbestos are carcinogenic. Such a tendency represents a misuse of the statistical and epidemiological data upon which the evidence is based.
>
> "It should be remembered that... (with few exceptions), the evidence supporting a causal relationship between a particular substance and the incidence of lung cancer is limited usually to the occurrence or use of that substance in only one of the many industries in which it may be present....
>
> "The possibility must be considered that there is a factor or factors common to all the industries concerned. The observations of Faulds and Stewart (4-f) in their studies on hematite miners have focussed attention again on the possible association between chronic irritation -- either mechanical or infective -- scarring and neoplastic change."

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ADVENT OF AUTOMOBILE PARALLELS LUNG CANCER INCREASE

C. O. S. BLYTH BROOKE, of the Public Health Department, Finsbury Health Center, London, England, reported on "The incidence of cancer of the lung 1932-1956" for England and Wales in 1958 (24-b). Quotes from his paper follow:

> "It is clear that other factors are concerned in the phenomenal rise of the death rate from cancer of the lung in recent years apart from that of smoking, however firmly its relationship with the latter be regarded as established....
>
> "The investigation reported here has been pursued in a search for evidence of the time when the first changes occurred which led eventually to the manifestation of lung cancer and death from this cause....
>
> "The findings here reported indicate that the development of cancer of the lung now seen may have been at least partly determined during the 'teen ages....
>
> "The suggestion is made that one explanation of available data is that early in the century there was an almost explosive increase in the bronchocarcinogenetic forces. It is not the purpose of this report to discuss the nature of these forces which might have operated or their origin, but thoughts turn involuntarily towards the rapid development at that time of motor-car traffic."

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MANY LUNG CANCER DEATHS NOT ACCOUNTED FOR

A study was made of the mortality of men aged 45 to 64 from various respiratory diseases, including lung cancer, by economic class and also in contrast to levels of air pollution from domestic chimneys and industry in 83 country boroughs of England and Wales where they lived. Charles DALY of the Social Medicine Research Unit of the British Medical Research Council, reported in 1959 (1-d) that only 35% of variations in lung cancer incidence between the towns could be attributed to the combined effect of both pollution and social conditions. He said it was impossible to track down most of the remaining 65% discrepancy. He reported:

> "As far as the proportions of non-smokers and cigarette smokers only are concerned, there is little indication that the average amount smoked varied very much from one group of towns to another. At the most, if we consider the number of cigarettes smoked per male in these groups of towns, we get an increase of about 18% related to a 63% increase in the lung cancer death rate. It may be, of course, that an index of present smoking habits is inadequate and that a measure of smoking habits 30 years ago is more relevant here. That may be so: but to explain away the differential in lung cancer death rates between towns in terms of smoking habits would imply that substantial changes had taken place in the smoking habits of the populations in whole groups of towns....
>
> "It seems likely, therefore, that neither differences in domestic or industrial air pollution, in smoking habits, or in social factors can account for more than a relatively small proportion of the variation observed in the death rates for lung cancer in the various county boroughs. In seeking for some other factor which could be responsible for the variation, a number of analyses were carried out. One interesting result which emerged was the fact that lung cancer seemed to be highly related to respiratory tuberculosis, in so far as those towns with a high death rate from one disease tended also to have a high death rate from the other."

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I-C 5

OCCUPATIONAL CANCERS LISTED

T. M. FRASER, M.B., Ch.B., Resident in Aviation Medicine, B. D. DINMAN, M.D., Associate Professor, and W. F. ASHE, M.D., Professor and Chairman of the Department of Preventive Medicine, Ohio State University School of Medicine, reviewed the literature on occupational cancer (12-f) from the finding of scrotal cancer in chimney sweeps (20-p), through the successive incriminations of paraffin from coal, arsenic, excessive sunlight, dyes, x-rays, chromates, nickel, asbestos up to isopropyl alcohol in 1952. They continue:

> "These are by no means all of the cancers whose origin has been attributed to occupation. Legal files are filled with allegations of cancer produced by a single trauma.... It is evident that occupational cancer exists, and before we can prevent it or protect against it, it behooves us to learn how many varieties there are, to observe where they occur, and to define the etiology as precisely as possible.
>
> "When considering occupational cancer of the respiratory system, which in this context includes the tract from the nose and paranasal sinuses to the alveoli, it is pertinent to observe that there has been a considerable overall increase in the incidence of lung cancer during the past 25 years. How much of this is due to improved diagnosis and greater frequency of autopsy and how much to atmospheric pollution, increased exposure to occupational carcinogens, and other as yet unknown factors can only be a matter of opinion."

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ENVIRONMENT AND OCCUPATION IN LUNG CANCER

W. C. HUEPER, M.D., Head of the Environmental Cancer Section of the National Cancer Institute, with a background of 35 years of clinical, teaching, and research experience, analyzed many factors in environmental and occupational lung cancer in a Monograph published in 1956 (35-h). He said:

> "Epidemiological studies on the frequency of lung cancer among members of large industrial groups and trades have brought to light the existence of marked variations in the liability of persons engaged in different occupations to cancer of the lung.... (A listing of) lung cancer death rates for seven industrial groups in Ohio shows a striking difference between the rates for agricultural laborers and for employees in the non-ferrous metal industry, with rates for transportation workers occupying a position directly behind the rates for nonferrous metal workers.
>
> "It seems to be characteristic of inhabitants of agricultural areas to rank first in death rates from cutaneous cancer and last in rates for pulmonary cancer. This is in accordance with the relationship between solar radiation and skin cancer and the relationship between low concentrations of carcinogenic air pollutants and lung cancer.
>
> "Nonferrous metal workers, on the other hand, often have contact with dust, fumes, and vapors of some carcinogenic metals, such as chromium and nickel, or with arsenicals which are impurities in many nonferrous metals (copper, zinc, silver). Transportation workers are exposed to the exhaust from gasoline and diesel engines, petroleum lubricants, and dust from asphalted roads....
>
> "The comprehensive panoramic view and analysis of the total epidemiological, medical and experimental evidence available on exogenous respiratory carcinomas and carcinogens leave no doubt of the fact that not only large occupational population groups but also the general population have definite and prolonged contacts with one or several of these agents.
>
> "For most of these agents, adequate conclusive proof of their carcinogenicity is provided by epidemiological, medical and experimental data...."

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"It is therefore reasonable to assume that inhalation of the same agents, in a mitigated form as air pollutants, by the general population is responsible for a considerable portion of the lung cancers attributable to such contacts.

"If this coherent and logical picture presented by the evidence supporting the various occupational respiratory cancers and, especially, the coal tar fume cancer of the lung, is compared with that available for the cigarette smoke lung cancer, even upon superficial examination, several additional serious defects and inconsistencies not previously pointed out become apparent.

"It is surprising to note the absence of positive statistical associations between lung cancer and cigarette cough, although this latter symptom is clinically characteristic of chronic chain smokers. Despite the fact that the lips and oral mucosa are constantly bathed in the tarry liquor oozing from the lip of the cigarettes and despite the contact of these parts with the smoke coming from the cigarettes, there is no consistent statistical association with cancer of these parts. The assertion that no tarry material exudes from the cigarette tip is belied by the evident fact that chronic cigarette smokers are observed to have brown-stained fingers. There is, on the other hand, not a single record available of cancer of the fingers attributable to cigarette tar. Such cancers of the fingers would be equivalent to the numerous cases of coal tar cancers of the hands for which records are available...."

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"The best that can be said about the experimental evidence on hand regarding carcinogenic properties of tobacco tar is that it indicates the carcinogenic agents in some cigarette tars through the use of hyperreactive animals. There is no evidence that these observations of the skin of a strain of selectively inbred mice have any equivalent in man....

"For these reasons, it would be most injudicious mainly to base the future preventive control of lung cancer hazards on a theory of such doubtful scientific merits and to concentrate the immediate epidemiological and experimental efforts on this apparently overpropagandized concept. The apparent wisdom of such an attitude is readily apparent from the fact that not only a great deal of the circumstantial epidemiological evidence but also practically the entire factual and conclusive evidence available on specific exogeneous causes of respiratory cancers indicates that these cancers are either of occupational origin or points to industry-related factors. Not only large occupational groups but also the members of the general population have contact with these agents in various forms and intensity."

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RADIATION
A CAUSE OF
LUNG CANCER?

Egon LORENZ, Senior Biophysicist of the National Cancer Institute at Bethesda, Md., discussed the biologic effects of long continued irradiation in 1950 (22-1). He had previously (21-1) concluded from a review of the experimental data that "it is doubtful whether radon can induce lung tumors in experimental animals," and that "the opinion that radon is the sole cause of the lung cancer of the (Schnesberg-Joachimsthal) miners therefore cannot be maintained." His 1950 report was based on nine years of experimental study of "permissible" doses of x-ray exposure in animals. He said in part:

> "Lung tumors occur spontaneously in a number of strains of mice. They are of alveolar origin, develop slowly, and rarely cause death. Hence incidence data in experiments covering the whole life span are merely suggestive. To obtain quantitative data, an experiment was performed in which mice of strain A, which is the most susceptible strain known, were exposed chronically to an accumulated dose of approximately 2,500 r given at the rate of 8.8 r in eight hours daily.... 75% of the irradiated animals showed lung tumors as compared with 45% of the non-irradiated group.... Data obtained thus far indicate that lung tumors are induced by a direct effect of the irradiation on the lung and that no systemic effect is involved....
>
> "The carcinogenic action of chronic irradiation has been observed in three species, one of which, the guinea pig, is considered one of the least susceptible animals to spontaneous tumor formation. It seems that we are justified in assuming that this carcinogenic action of chronic irradiation will hold for other species as well as for man. We are just beginning to acquire some information as to the mechanism of tumor induction, or more specifically regarding the role which the endocrine system plays in radiation carcinogenesis of certain organs, but we are still a long way from understanding the fundamental process by which irradiation changes a normal cell into a cancer cell."

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For other papers on occupational and environmental factors in lung cancer etiology see 6-b, 17-b, 22-b, 26-b, 27-b, 33-b, 41-b, 2-c, 35-c, 14-c, 3-d, 29-d, 5-d, 8-d, 1-e, 2-e, 3-f, 4-f, 7-g, 8-g, 9-g, 31-g, 10-g, 11-g, 21-h, 26-h, 32-h, 33-h, 34-h, 36-h, 37-h, 44-h, 2-l, 3-l, 4-l, 6-l, 3-m, 13-m, 14-m, 15-m, 16-m, 17-m, 31-m, 34-m, 41-m, 42-m, 14-p, 22-p, 24-p, 26-p, 27-p, 1-s, 2-s, 3-s, 5-s, 16-s, 4-t, 5-t, 5-v, 15-w

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D. LUNG CANCER IS RELATED TO STRESS, VIRUSES, HORMONAL DISTURBANCE AND GENETIC FACTORS

The magnitude of what is still unknown--in lung cancer as in other basic biological problems--becomes apparent when we survey even a fraction of the recent studies on possible causes. No possible mechanism--internal or external, genetic or environmental, infectious or physiologic--goes unrepresented; there is evidence for them all.

Thus the number of identified viruses known to cause cancer in experimental animals has increased astronomically with recent improvements in laboratory and experimental methods. Demonstrations of associations between lung cancer and prior viral diseases are spurring research in this area.

On another front, evidence of the potent role of hormones, and other mediators of the internal environment, in the early stages of carcinogenesis is accumulating steadily. An increasing body of study links hormonal changes with human stress, and stress with the behaviors peculiar to the complex structure of modern civilization.

Thus, smoking, drinking and other pursuits are considered to be as much a reflection of the special environment of the individual as are the states of his health, and "cause-and-effect" arguments may link what is merely concurrent: the man who is likely to develop cancer of the lung as a result of severe stress and functional disturbances may be the kind of man who will smoke heavily. By the same token, functional and infectious diseases may be more likely to affect the "stressed" than the "unstressed" individual.

The following few selections are representative samplings of the extensive literature dealing with the varied factors suspected of cancer causation.

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VIRAL AND NON-VIRAL THEORIES RECONCILED?

Donato G. ALARCON, M.D., Fellow of the American College of Chest Physicians and Medical Director of the Sanatorio San Angel of Mexico City, reviewed Mexican lung cancer data in 1959 (7-a), and found a marked coincidence with the higher cancer-proneness of immigrants to a country than of natives reported by several authors (40-b, 3-d, 2-e, 13-m, 14-m, 6-r, 35-s, 36-s, 37-s) in South Africa, New Zealand, Israel and the United States. He visualized the possibility that a latent infection or exposure to a "foreign" virus to which no immunity existed in the immigrant might explain the susceptibility of the newcomer to cancer. He said:

> "Search for causes of cancer of the lung has been focused on two groups of admittedly responsible factors: intra- and extra-cellular ones. The first group includes: a) hereditary and b) enzymatic, and other factors. The second group includes: a) physical, b) biological and c) chemical agents.
>
> "The hereditary factor is well-known from the study of neoplasms in animals. Some strains of laboratory animals are more prone to cancer than others. These strains have been bred for research purposes.
>
> "In order to explain the mechanism of transmission of certain biological agents (i.e., viruses) it has been postulated that they act on the chromosomes, bringing about changes in the genes which virtually convert the gene into a gene-virus capable of transmitting mutation through generations. This theory has sought to reconcile the viral and non-viral theories of the origin of cancer...
>
> "Less known and less extensively studied factors than those included in the intra- and extra-cellular groups are of much interest. They are those which may cause the great variation in geographical incidence of cancer. Moreover, certain migratory movements reveal differences in the incidence of cancer among natives and immigrants in various countries....

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"A viral infection, incurred prior to emigration, latent, like many viral infections, for long periods of time until a sudden provocation arouses the neoplasm to activity -- such an hypothesis may explain the difference; or else, exposure to foreign viruses to which no previous immunity exists....

"To this attractive hypothesis the new knowledge of the experimental concepts of latency, inhibition and masking of viruses as expounded by Huebner 40-h , Andervont 12-a, Goodpasture 24-g in 1957 give support to the possibility of a dormant viral infection as a factor for the development of cancer of the lung."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

I-D 3a

HEREDITY, AGE AND HORMONE INFLUENCES ON VIRAL CANCER

Howard B. ANDERVONT, Sc.D., of the National Cancer Institute, Bethesda, Md., in 1957 (12-a) reviewed the marked degree of association of genetic, hormonal and age factors with virus induced cancers in various species and strains of laboratory animals, and the bearing this research may have on solving human cancer problems. He said:

> "Many factors are involved in the maintenance or alteration of the host-virus relationships which influence the occurrence of virus-induced tumors. The purpose of this paper is to discuss briefly three factors, namely genetic, hormonal, and age, which are known to exert a pronounced influence upon the susceptibility of experimental animals to the development and transplantation of these tumors....
>
> "The importance of genetic factors in virus-induced tumors are best understood in the laboratory mouse, for the simple reason that highly inbred strains of these animals are available which permit the investigator to evaluate the influence of a virus upon animals of known genetic constitutions....
>
> "The age of the host is often crucial in heterologous transmission of viruses and most successful efforts to overcome species resistance to tumor viruses are dependent upon the use of young experimental animals.... Age factors in susceptibility to viruses probably reflect the inability of newborn and young animals to produce antibodies, or, with the viruses of chicken lymphomatosis and mouse mammary tumor, the young are highly susceptible to a virus which remains quiescent for months before tumors occur....
>
> "Hormonal stimulation is important in many forms of cancer including some virus-induced tumors.... Extensive studies have been made of hormonal factors influencing leukemias and mammary tumors in the mouse, and there are several good reasons for such studies.

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"(1) The tumors arise spontaneously in a common laboratory animal. (2) They usually occur spontaneously in middle or late life or, when induced with viruses, the incubation periods extend over months. (3) They do not appear at the site of inoculation; a characteristic which could make them more responsive to hormonal activity than those tumors occurring promptly at the site of administration. (4) Of most importance, they are studied in inbred strains of animals showing a high or low incidence of tumors in which the relationship between virus, genetic factors, and hormonal factors can be accurately determined....

"Genetic, hormonal age factors are important in the occurrence and growth of many tumors in experimental animals. The fact that the influence of these factors is not limited to virus-induced tumors indicates that tumors of known viral etiology should not be considered as belonging to a distinct or peculiar group of neoplasms. Indeed, the diversity among virus-induced tumors is sufficient to include all types of experimental tumors....

"The specificity of tumor viruses has been one of the major obstacles facing those who attempted to detect a virus in human tumors.... In brief, the growing ability of investigators to surmount genetic factors by the use of newborn animals and by hormonal stimulation may enable them to transmit tumor viruses of one species to another species."

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CHROMOSOMAL ABNORMALITY IN LEUKEMIA

A. G. BAKIE, M.B., W. M. COURT BROWN, M.B., Patricia A. JACOBS, B.Sc., of the British Medical Research Council group for research into the general effects of radiation, at Western General Hospital, Edinburgh, and J. S. MILNE, M.B., general practitioner in East Lothian, Scotland, collaborated in chromosome studies in human leukemia reported in 1959 (2-b).

They said:

> "The occurrence in neoplastic cells of chromosome abnormalities, both of number and form, is now well established, although their frequency and significance in relation to carcinogenesis remains uncertain....
>
> "Three possibilities may be considered. Firstly the chromosome changes may arise as epiphenomena in a grossly disordered bone-marrow; secondly the visible chromosome changes may include the fundamental change which has conferred neoplastic qualities on the marrow cells; and thirdly it is possible that the chromosome changes are the consequences -- perhaps the remote consequences -- of a more subtle alteration in the genetic constitution of the leukemic cell. This last interpretation seems the most likely."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

CANCER CAUSES UNKNOWN: DATA ON VIRAL ORIGINS INCREASING

W. Ray BRYAN, of the Laboratory of Biology, National Cancer Institute, Bethesda, Md., in 1960 (57-b) presented a reconsideration of the nature of neoplasia in the light of recent advances in cancer research:

> "It is now widely recognized that cancer is not a single disease, but a group of diversified diseases having certain pathological manifestations and dynamic biological properties in common....
>
> "By far the greatest majority of spontaneously occurring human neoplasms are associated with etiological agents that are still unknown (Boyd, 1953) (56-b). The possibility that viruses may be involved in the human diseases to a considerable degree is suggested by the discovery of many new tumor viruses of laboratory animals during the last few years."

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ROLE OF VIRUS IN TUMORS AND INFECTION

Leon DMOCHOWSKI, M.D., Ph.D., of the University of Texas M.D. Anderson Hospital and Tumor Institute and Baylor University College of Medicine, Houston, reviewed 454 papers treating of viruses and tumors in 1960 (27-d). He said:

> "Electron microscopy has... undoubtedly contributed to present-day knowledge of all cell structure by revealing an essential similarity of the structure of cells of plants, animals, and man. It has further shown that cellular components have certain physiological and chemical functions.... Present-day electron microscopy has shown that viruses are not molecules, as at first considered when tobacco mosaic virus was crystallized, but have a complicated structure like that of cells. It has helped to show the basic constituents of specific activity of viruses and their localization within a virus particle.
>
> "When one has learned that nucleic acids are the basis of viral activity, the question arises whether or not the nucleic acids, especially deoxyribonucleic acid, are responsible for the malignant change.... The part played by a virus in infection or tumor induction may at first sight appear to diminish in favor of its component -- the nucleic acid; in other words, the part played by the virus may be merely that of a postman delivering a message. However, it still remains to be shown that infection or tumor induction by nucleic acids can occur under natural conditions.
>
> "The nucleic acids, at least under experimental conditions, have been shown to form the basis of a new approach to the study of disease in general and of tumors in particular. Only a combination of morphological, biochemical, biophysical, and perhaps some new, as yet unknown, methods will show whether we have, indeed, landed or have been stranded at the molecular level. The constant realization, however, that no matter what happens at the molecular level, it is the cell and the host which eventually becomes afflicted with cancer, may lead to a true understanding of neoplastic disease."

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CANCER FACTS ACCEPTED BY BIOLOGISTS

Jacob FURTH, M.D., of Harvard Medical School, in his Presidential Address before the American Association for Cancer Research in 1959 (20-f), said that "one-sided theories" arise as scholars in diverse disciplines pursue various leads with their own techniques, hence there is an "eternal need for a meeting of the ways" among scientists.

> "So arise one-sided theories: cancer is a virus disease, or an abnormal differentiation, or a somatic mutation, or an immunologic disorder, or a self-perpetuating defect in oxidative metabolism, or an adaptive deletion of a cell component.
>
> "Any of these theories may be overwhelmingly true within the horizon of one discipline. But they appear faulty on many scores when considered by scholars of other disciplines as the universal basis of the many diseases named cancer. On the other hand, such theories do elucidate some features of some cancers and thus need not be discouraged....
>
> "The following appear to us cancer biologists to be established facts about cancer:
>
> "1. Neoplasia is a state in which cells, normally limited, proliferate with no restraint.
>
> "2. This state can be brought about by changes either in host or in the cell. The former type of neoplasm is termed dependent, the latter autonomous.
>
> "3. The basic derangement in the host can be due to sustained excessive stimulation or to a deficiency of natural restraining forces.
>
> "4. The basic derangement in the cell can be cytogenic, or it can reside outside the self-replicating apparatus of the cell, as in parasitism by virus. The former is an autonomous, the latter a virus-dependent, neoplasm.
>
> "5. Some autonomous tumors respond in varying degrees to their physiologic regulators; others do not.
>
> "6. The trend is for progression 'from bad to worse;' from good to poor responsiveness; from nearly normal function to no function."

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VIRAL AGENTS
IN HUMAN TUMORS
CAUSE MICE CANCERS

James T. GRACE Jr., M.D., and his colleagues Drs. Edwin A. MIRAND and Joseph A. DiPAOLO at the Roswell Park Memorial Institute, Buffalo, N.Y., have found viral agents, seemingly capable of producing cancer in mice, in human tumors (13-g). As recounted by the New York State Department of Health Bulletin, they said:

> "There appears to be a definite relationship between injection of human tumor extracts and appearance of tumors in mice.... (We are investigating) the possibility that oncogenic viruses are implicated."
>
> Of 606 mice receiving direct inoculation of unfiltered human tumor extracts, 26 developed cancer, as did 47 of the 791 mice receiving filtered extracts. Some mice developed four to six cancers. No tumors appeared in mice injected with healthy human tissue culture preparations.
>
> From this, the researchers concluded that "normal human tissue is not related to the appearance of animal tumors, at least not under the time limits of these studies..... (Results of the study showed) no correlation between the type of human tumors employed and the types of tumors appearing in mice." The greatest number of cancers in mice, mostly breast tumors of pregnant mice, resulted from injections of extracts from persons with acute leukemia.

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I-D 7

HEREDITY AND CANCER

P. C. KOLLER, Ph.D., D.Sc., Professor of Cytogenetics, Institute of Cancer Research, Royal Cancer Hospital of London, England, discussed heredity and cancer in 1959 (8-k). He says:

> "A summary has been made of our knowledge of the inheritance of susceptibility to cancer in mice and men. It has been pointed out that in both organisms the mode of inheritance is usually complex, involving a large number of genes. In man it has been shown that there is probably a strong inherited predisposition to cancer in certain sites, particularly the stomach and breast and to a less extent the cervix and uterus. Incidence of tumors at other sites has been insufficiently investigated from the hereditary point of view. It remains to be seen, for instance, whether it will be possible to demonstrate a hereditary component to cancer of other parts of the body such as the lung and the bladder.
>
> "The evidence from studies of twins lays more stress on the importance of the environment in the etiology of cancer and shows how in most cases identical susceptible genotypes do not meet with exactly the same environments. Racial differences in the frequency of incidence of cancer are not well documented and it is not easy to partition the hereditary and environmental components of susceptibility. But again the stress must be laid on environmental factors, particularly in considering such a genetically heterogeneous population as the human race."

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I-D 7a

EMOTIONS AND CANCER

Charles T. BINGHAM, Blue Hills Hospital, Hartford, Conn., in 1960 (55-b) told the Anniversary Congress of the Pan American Medical Association in Mexico City that there is much evidence that emotion plays a large part in the etiology of cancer:

> "Since hormones and virus infections and oxygen supply are all known to play some part in cancer growth, emotional stress must be considered too. The evidence... must be sought for in the case histories of people who have died from cancer, and it should be looked for in the environment, the personality and the background of the patient....
>
> "When stress factors have sensitized a certain tissue unit, symbolically-determined by the subconscious operation of the brain, it becomes vulnerable to tissue change.... Good emotions such as hope and faith and love certainly lead to health -- obviously bad emotions such as fear, anger, resentment, guilt, shame, etc., are very unhealthy. This paper deals with the influence of these bad emotions on the development of cancer in specific areas of the human body in specific individuals."

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PSYCHOLOGICAL FACTORS IN CANCER

Lawrence LeSHAN, Ph.D., of the Institute of Applied Biology, New York City, reported on extensive research into psychological states as factors in the development of malignant diseases in 1959 (8-e). Quotations from his paper follow:

> "When a field is in its infancy as this one is, with many lines of investigation proceeding simultaneously, and before any over-all body of theory has been formulated, it is extremely difficult to sum it up briefly. In trying to evaluate the present situation in this area, certain factors appear to emerge:
>
> "1) There seems to be a correlation between neoplastic disease and certain types of psychological situations. This has been widely reported as a result of clinical observations, experimental studies, and statistical investigations.
>
> "2) The most consistently reported psychological factor has been the loss of a major emotional relationship prior to the first-noted symptoms of the neoplasm. It seems to be established that this has occurred more often in cancer patients than in the various groups who were used as controls.
>
> "3) There appears to be some relationship between personality organization and the time from the first-noted symptoms of a neoplasm until the patient dies.
>
> "4) There may be some relationship between personality organization and the type or location of a neoplasm. The evidence that different types of people tend to develop different types of cancer is extremely suggestive.
>
> "The data and leads so far produced in this field seem worthy of further investigation. This is an exciting and stimulating field which is bound to lead into many provocative problems, and may point the way to new means of approaching the neoplastic process."

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ORIGINS OF HUMAN CANCER

Sir Heneage OGILVIE, M.Ch., KBE, LL.D., FRCS, Consulting Surgeon at Guy's Hospital, London, England, drew upon a lifetime of medicine and surgery for views on psychological factors in carcinogenesis, published in 1957 (2-o). He said:

> "Like most general surgeons, I have treated and watched many cases of cancer. Some were relatives; many were friends; others, coming as patients, died my friends. I have slowly come to frame in my mind an aphorism that never can be stated as such, because no statistics can be advanced to support it: 'The happy man never gets cancer.'....
>
> "The instances where the first recognizable onset of cancer has followed almost immediately on some disaster, a bereavement, the break-up of a relationship, a financial crisis, or an accident, are so numerous that they suggest that some controlling force that has hitherto kept this outbreak of cell communism in check has been removed.
>
> "The late appearance of secondaries, suggesting that over the years some undetected cancer cells have been lying latent and kept in check by some unknown restraining force, is a commonplace after operations for cancer of the breast. Very often -- indeed, so often as to suggest that if the true cause could be discovered the problem of cancer treatment might be solved -- the signal for renewed growth seems to have been some unhappy event."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

THE VIRUS THEORY OF CANCER

Wendell M. STANLEY, Ph.D., Professor of Biochemistry and Director of the Virus Laboratory at the University of California at Berkeley, Nobel Prize winner in chemistry in 1946, discussed the virus etiology of cancer in 1957 (33-s). He said:

> "Evidence for the virus etiology of cancer has come from so many different laboratories and has been of such good quality and quantity that I find it very difficult to understand why so many investigators have continued to have such a firm blind spot with respect to the virus causation of cancer. Many investigators accept viruses as etiological agents for animal cancers but are unwilling to consider them of etiological importance in cancers in man....
>
> "Recent advances in the cultivation of human cells in vitro and especially in the newer knowledge of certain properties of viruses warrant today a marked change in our thinking on the problem of human cancer. The time has come when we should assume that viruses are responsible for most, if not all, kinds of cancer, including cancer in man, and design and execute our experiments accordingly....
>
> "The recent findings in the virus field indicate more and more that the virus problem and the cancer problem are one and the same. The experimental evidence now available is consistent with the idea that viruses are the etiological agents of most, if not all, cancer, including cancer in man. Acceptance of this idea as a working hypothesis is urged because it will result in the doing of experiments that might otherwise be left undone, experiments that could result in the solving of this great problem. The past few years have seen the development of important new tools, and if we take full advantage of these we could easily tip the scale towards the solution of the cancer problem."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

GENETIC CONCEPT OF CANCER

The genetic concept for the origin of cancer has been the lifework of Leonell C. STRONG, Sc.D., Ph.D., in recent years working at the Biological Station, Roswell Park Memorial Institute, Buffalo, N.Y. In recent papers on this subject (43-s & 44-s) he said:

> "The various types of cancers which arise in the mammalian body have, at least, one characteristic in common. Cancer arises because the organism has lost control of a definitive part. Perhaps during the aging process the mechanism that keeps the individual in equilibrium is disrupted, and as a result of this loss of control of all the parts cancer of one or more elements is able to originate and to grow at the expense of the rest of the body." (43-s)

> "I... should like to reaffirm my faith in the genetic concept of the origin of cancer originally formulated in 1926 -- that a change comparable to a somatic mutation was involved. This change was defined as applying to any formed constituent of the cell, either nuclear or cytoplasmic, that could duplicate itself, affect the physiology of the cell specifically, and be transmitted by cell division." (44-s)

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

For further documentation on viruses as possible causes of human cancer and recent discoveries extending the range of known viral cancer see 1-a, 4-a, 11-a, 12-a, 6-a, 5-b, 82-b, 78-b, 79-b, 69-b, 55-b, 57-b, 80-b, 81-b, 42-c, 35-c, 26-d, 22-d, 9-d, 27-d, 20-d, 35-f, 36-f, 19-f, 26-f, 13-g, 34-g, 20-g, 6-k, 22-k, 64-m, 1-o, 46-p, 35-p, 12-p, 48-p, 19-p, 21-p, 35-r, 40-r, 22-r, 36-r, 42-r, 43-r, 75-s, 31-s, 34-s, 68-s, 76-s, 42-s, 77-s, 6-t, 13-t, 11-v, 5-z

For other comments on stress and psychological factors in carcinogenesis see 10-a, 1-b, 16-b, 55-b, 23-b, 34-c, 7-e, 8-e, 9-e, 10-e, 12-e, 11-f, 13-f, 6-g, 23-h, 2-k, 7-l, 15-l, 9-m, 21-m, 26-m, 36-m, 4-p, 49-p, 28-s, 8-t, 13-w

For additional data on genetic, hormonal and other endogenous factors in cancer see 55-b, 20-b, 21-b, 29-b, 31-b, 41-b, 46-b, 47-b, 44-b, 45-b, 48-b, 9-c, 20-c, 2-d, 3-f, 27-f, 10-f, 17-g, 2-h, 3-h, 4-h, 24-h, 38-h, 54-h, 5-k, 11-k, 12-k, 1-l, 16-l, 17-l, 5-m, 4-m, 8-n, 28-p, 33-r, 27-r, 23-s, 78-s, 24-s, 25-s, 27-s, 30-s, 34-s, 55-s

For studies on psychological and physiological differences between smokers and non-smokers see 12-e, 10-f, 20-h, 15-l, 16-l, 18-l, 21-m, 23-m, 14-s

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II.

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II. WHO GETS LUNG CANCER?

Why do a few persons get cancer of the lung while most people do not? Why are men more frequently affected than women? What kind of differences are there between groups with high lung cancer death rates and those with low rates?

These questions arise from the fact that there are major differences in lung cancer mortality from country to country, from one region to another, between city and farming areas, between high income and low income groups, between males and females.

The pattern of lung cancer is, in short, very much of a jig-saw puzzle that creates more problems than it answers.

There is an extensive literature relating to each of these areas of contrasted data. Following are a number of representative studies that do not stop at describing the differences noted but that attempt to offer explanations or to point out suggested avenues of research. This will be followed by a bibliography of other papers relating to these subjects.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

LUNG CANCER HIGHER IN POORER CLASSES

Dr. Edward M. COHART of the Yale University School of Medicine, New Haven, Conn., found a socioeconomic distribution of lung cancer incidence in that city, according to a paper published in 1955 (12-c).

He says:

> "Two hundred and ninety-one cases of cancer of the lung, 235 in men and 56 in women, occurred in New Haven residents in the 15-year period between 1935 and 1949....
>
> "When the 291 cases were allocated by sex to the appropriate socioeconomic regions it was found that the incidence of lung cancer was about 40% greater among the poor....
>
> "Unless it is assumed that cigarette smoking is inversely related to socioeconomic status, an assumption that probably cannot be supported in fact, then it is reasonable to conclude that important environmental factors other than cigarette smoking exist that contribute to the causation of lung cancer."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

II 3

LUNG CANCER AMONG WHITE SOUTH AFRICANS

Geoffrey DEAN, M.D., MRCP, Senior Honorary Physician at the Provincial Hospital in Port Elizabeth, Union of South Africa, emigrated from Liverpool, England, to Port Elizabeth in 1947, and was surprised to find so few cases of lung cancer there, although cigarettes were cheap and most men appeared to be heavy smokers. In view of British and American statistical studies linking cigarette smoking to lung cancer, he undertook an investigation of these matters in South Africa (3-d).

He says:

> "1. White male South Africans have long been the heaviest cigarette smokers in the world, and yet they have a relatively low lung cancer mortality rate.
>
> "2. British male immigrants to South Africa who died between the ages of 45 and 64 had a much higher lung cancer rate than either white Union-born men or male immigrants from other countries for the same age groups. As most of the British immigrants came to South Africa before reaching middle age, British cigarettes are likely to have formed only a small percentage of the total cigarettes smoked by those dying of lung cancer at these ages. It is therefore unlikely that the difference in lung cancer mortality experience in these age groups is attributable to differences between South African and British cigarettes....
>
> "3. The excess lung cancer mortality among British male immigrants, as compared with Union-born white men, is found only in those dying of lung cancer under the age of 65. Above that age there is no significant difference between the lung cancer mortality rates in the two groups. This suggests, therefore, that the greater liability of the more recent British immigrants to lung cancer is a relatively new phenomenon, and that the immigrants were exposed to the etiological factor or factors concerned before they left Britain.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

"4. The higher incidence of lung cancer among residents in South African towns... as compared with the incidence among residents in rural areas, would seem to be strong evidence that atmospheric pollution is an important factor. If so, it is equally likely that the higher incidence among the more recent British immigrants may again be connected with the atmospheric pollution to which they were exposed before emigrating."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

II 5

LUNG CANCER MORTALITY IN NEW ZEALAND

David F. EASTCOTT, M.B., D.P.H., Assistant Director of the National Health Institute of Wellington, New Zealand, appreciated the epidemiological advantages possessed by his country in that virtually all white habitants came from the same stock, making it possible to compare cancer mortality among natives with that in persons who had lived under a different environment before coming to New Zealand (2-e). He says:

> "The following sites were considered at first, as well as deaths from cancer of all sites: stomach, large intestine, rectum, lung and bronchus, breast, cervix uteri, prostate, and skin.... Important unequivocal differences were found, however, in lung and bronchus only.... In the latter site the immigrant group has a much higher incidence of bronchogenic cancer than would be expected on the basis of equity, suggesting that for this site, and this site alone, the immigrant has an increased susceptibility....
>
> "The difference is greater in those who were aged 30 or more when they came to New Zealand. This increased incidence is unlikely to be an artefact, for it is not seen in any other of the principal sites for cancer. Moreover, it is the same for women as for men and is consistent at all ages over 35 and for all the principal parts of the country. The chances of dying of cancer of the lung are 30% higher for all UnitedKingdom immigrants, but for those who were 30 years of age or more on entering New Zealand the risk is 75% higher....
>
> "The conclusion follows that immigrants from Great Britain to New Zealand are affected by their former environment and that this effect is related to the length of exposure in that environment..... Differences in habits of tobacco smoking are unlikely to contribute to this picture. The evidence points to the factors being associated with urbanization, as has been suggested in other studies. It shows too that they may exert their carcinogenic effect a long time after the person has been removed from them, and this is in keeping with what is known of the mode of action of the carcinogens isolated from the atmosphere of industrial cities."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

MALE-FEMALE DIFFERENCES IN LUNG CANCER

G. HERDAN, of the Department of Public Health, University of Bristol, England, analyzed both the socioeconomic factors and also sex differences in British lung cancer incidence in 1958 (24-h). The greater number of reported cases of lung cancer in recent years may have brought to light by 1950 a social class gradient always inherent in lung cancer, but which was not perceptible in 1930, when the disease was frequently diagnosed as something else. As to the sex ratio, he said:

> "In man, the male is the heterogametic sex, and as such possesses one x-chromosome, whereas the female, as the homogametic sex, possesses two.... It follows that if a recessive gene for a certain disease or condition is carried in a different segment of the x-chromosome, it is at once uncovered in the case of the heterogametic individual, and if in its action such a gene is disadvantageous, deleterious or lethal, it will find expression in the phenotype of the individual....
>
> "This hypothesis is confirmed by the fact that increase of infant excess male mortality with time is, in general, accompanied by a decrease of the death rate of infants, males and females together.... As a consequence, the downward trend in the general mortality of infants should be accompanied by an upward trend of excess male mortality. This we find confirmed in all the countries for which we have data...
>
> "One obtains invariably a significant negative correlation, which may be regarded as support for the hypothesis that excess male mortality was due to innate differences between the sexes.... For lung cancer such a negative correlation can be established between the excess male mortality due to the malignant disease and the mortality for males and females combined due to inflammatory and infectious lung diseases, separately or combined.... There must be added the selective action (of the two World Wars) upon the male population of this country."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

MALE-FEMALE LUNG CANCER INCIDENCE

W. C. HUEPER, M.D., Head of the Environmental Cancer Section, National Cancer Institute, Bethesda, Md., commented on sex differences in lung cancer incidence at the Second National Cancer Conference in 1952 (32-h). Quotes from his remarks follow:

> "In contrast to the spectacular rise in the mortality from lung cancer in males, that of lung cancer in females is decidedly less impressive.... Assuming that cigarette smoking represents the predominating causal factor in the development of lung cancer in the general population during the last 50 years, one would have to expect that a narrowing of the gap between male and female lung cancer mortality during the last 10 years should be demonstrable.
>
> "The gap, however, is growing wider at a rather rapid rate. Although the larynx is part of the normal 'smoke tract,' there is no indication of a significant increase in larynx cancer mortality for both sexes during the last 25 years. The negative epidemiologic observation also does not favor a dominating role of cigarette smoking in the production of lung cancer.
>
> "Table I demonstrates that there existed an appreciable annual increase in lung cancer mortality for over 40 years and that the increment was apparently larger during the first 25 years of this century than during the second quarter. If cigarette smoking would be the main causal factor in bringing about the progressive rise in lung cancer incidence, one would have to assume that the increment would have shown an increase rather than a decrease during the second quarter."

Table I. Annual Age Adjusted Increase in Frequency of Lung Cancer Mortality

	Dorn		Potter
	1914-1930	1931-1940	1933-1944
Males	10.5%	8.5%	5.8%
Females	8.0%	2.5%	2.0%

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

MALE-FEMALE LUNG CANCER INCIDENCE

Helen KIRCHOFF and R. H. RIGDON, M.D., Head of the Department of Pathology at the University of Texas Medical Branch, Galveston, reviewed 147 papers on the incidence of bronchial carcinoma in 1959 (4-k). They said:

> "Much of the confusion in this controversy has arisen because statisticians have obtained the frequency of the occurrence of lung cancer from death certificates without taking the opportunity to follow a series of diagnostic problems, such as lung cancer, through the course of hospitalization and the post-mortem to see the difficulties that arise in establishing the cause of death. The chance for errors to arise from data obtained from autopsies could not be any greater than those inherent in vital statistics....
>
> "From the available data it appears that the increase in lung cancer has been greater in the male than in the female. However, the question may be asked -- how much of this difference is real, and how much is only apparent? This review shows the state of confusion referable to the incidence of lung cancer in the male and female.... It would appear from this review that the male-female ratio of lung cancer was approximately 3 or 4 to 1 in 1900 and 5 or 6 to 1 in 1955."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

CANCER MORTALITY AMONG NATIVE AND FOREIGN BORN RESIDENTS OF OHIO

Thomas F. MANCUSO, M.D., M.P.H., Chief of the Division of Industrial Hygiene, and Elizabeth Jackson COULTER, Ph.D., Chief Statistician, Ohio Department of Health, in 1958 analyzed mortality of men aged 25-64 from cancer of the lung, the larynx and the bladder for 1947-51, and from tumors of the central nervous system for 1944-52 (14-m). They said:

"Mortality was higher among foreign-born white males than among native white males for each of the four cancer sites in the 25-to-64 year age range. The difference was relatively larger for cancer of the lung and larynx than for either of the other sites....

"Lung cancer death rates per 100,000 population were as follows for Ohio for the years 1947-51:

Nativity	White males.... age groups			
	45-49	50-54	55-59	60-64
Native	22.16	44.28	55.23	74.83
Foreign-born	25.99	70.72	109.17	138.17

"Previous investigators have noted an association between socio-economic status and cancer (14-k, 21-r). An earlier report on cancer in Ohio indicated that in Cuyahoga County, high lung cancer mortality among white males was associated with low economic status, low educational level, and foreign birth (13-m)....

"Mortality of the foreign-born white male residents of Cuyahoga County varied considerably by country of birth. For example, lung cancer mortality was higher than expected among males born in Poland, Yugoslavia, and the U.S.S.R. and relatively low among Irish and Italian males. Mortality due to cancer of the larynx was particularly high among males born in the U.S.S.R.... On the other hand, the lung cancer mortality rate among male immigrants... from England and Wales was similar to the mortality rate due to this cause among native white males of Cuyahoga County but was considerably lower than among the male population of England Wales."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

II 10 Sub.

VARIATIONS IN WHITE MALE LUNG CANCER MORTALITY IN METROPOLITAN AREAS

Nicholas E. Manos, Chief Statistician of the Air Pollution Medical Program, U.S. Public Health Service, in 1957 published a study on "Comparative Mortality Among Metropolitan Areas of the United States -- 1949-51 -- 102 Causes of Death" (16-m). This was supplemented by a special study which combined the lung cancer data, which the original report divided between "malignant neoplasms of trachea, bronchus and lung, specified as primary" (International Statistical Classification of Causes of Death -- ISC -- #162) and "malignant neoplasms of lung, unspecified as to primary or secondary" (ISC #163). The "Supplemental Tables" were published in 1962 (73-p), for the following reason: "The separate mortality ratios published for each of these two causes have not been of maximum value because in practice reported deaths from lung cancer unspecified (ICS #163) include varying proportions of deaths from primary lung cancer in different areas."

Selections from all three sets of data are provided herewith for white males only, first for the 20 largest metropolitan areas, and next for certain pairs of cities that show striking differences in lung cancer mortality, although they have approximately the same white male population. The first column gives the white male population for 1950, and the 2nd, 4th and 6th columns the ratios of age-adjusted cause-specific mortality for each metropolitan area to the mortality experience for the total United States population. The 3rd, 5th and 7th columns are the present compiler's figures which show the extent to which the ratios exceed or fall below the average mortality rates for the entire United States.

The combined population of all 163 metropolitan areas in the survey was 85,527,096 in 1950, or 56.4% of the entire U.S. population.

Another fact brought out by the study is a tabulation of age-adjusted mortality rates by "degree of urbanization": the annual mortality rate for primary cancer of the trachea, bronchus and lung among white males was 11.5 for central city counties, 9.0 for non-central city counties included in the report, and 5.8 for non-metropolitan counties. For cancer of the lung unspecified, the figures were 13.9, 14.1 and 8.6 respectively. The Supplemental Tables do not provide these data. The data for women were less marked: 1.6, 1.3 and 1.2 for primary and 3.0, 2.7 and 2.7 for unspecified lung cancer, respectively.

The study was undertaken as a guide to the possible effects of air pollution on U.S. mortality from many causes, including lung cancer. "The reason for excesses of mortality in particular areas is often obvious," the original study says. "Sometimes they are due to the concentrations of certain occupational groups; in other cases, persons with existing disabilities have tended to migrate to certain areas. Where the reason is not immediately identifiable, the excesses provide an area for research on the influence of environmental and other factors."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

II 11 Sub.

Among the interesting questions raised by these tabulations are the following:

Why did Los Angeles physicians specify "primary" lung cancer 80% more than the whole nation and "unspecified" lung cancer 40% less, while Boston doctors did just the reverse: "primary" lung cancer was 20% under the nation, "unspecified" lung cancer was 40% more? (Note that by combining the data, they came out even: both were 10% above the national lung cancer average).

Why did similar differences distinguish Denver from Dallas? Denver is a noted center for respiratory tuberculosis.

Why was Baltimore more lung cancer prone than the Twin Cities? Or the Albany-Schenectady-Troy area than Youngstown, Ohio? Or Norfolk-Portsmouth than Akron? Or New Orleans than San Antonio? Or Springfield, Ill. than Altoona, Pa.? Or Columbus, Ga. than Greenville, S.C.? Or Charleston, S.C. than Augusta, Ga.?

Why did physicians in Birmingham, Ala. and Columbus, Ga. report extraordinarily high rates for "primary" lung cancer and less than half the national level for "unspecified" lung cancer?

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

II 12 Sub.

20 Principal Metropolitan Areas

Lung cancer, code numbers:	White Male Population	ISC #162 Ratio to U.S.Total	ISC #162 Comp. to par	ISC #163 Ratio to U.S.Total	ISC #163 Comp. to par	ISC #162 & 163 Ratio to U.S.Total	ISC #162 & 163 Comp. to par
N.Y. City	4,238,175	1.5	+ 50%	1.7	+ 70%	1.6	+ 60%
Chicago	2,423,596	1.4	+ 40%	1.3	+ 30%	1.3	+ 30%
Los Angeles	1,973,076	1.8	+ 80%	0.6	- 40%	1.1	+ 10%
Philadelphia	1,565,483	1.5	+ 50%	1.2	+ 20%	1.4	+ 40%
Newark-Jersey City	1,547,091	1.2	+ 20%	1.7	+ 70%	1.5	+ 50%
Detroit	1,337,805	1.2	+ 20%	1.3	+ 30%	1.3	+ 30%
Boston	1,356,582	0.8	- 20%	1.4	+ 40%	1.1	+ 10%
San Francisco-Oakland	1,019,594	1.4	+ 40%	1.2	+ 20%	1.3	+ 30%
Pittsburgh	1,028,200	0.9	- 10%	1.2	+ 20%	1.1	+ 10%
St. Louis	711,403	1.2	+ 20%	1.4	+ 40%	1.3	+ 30%
Cleveland	641,256	1.3	+ 30%	1.4	+ 40%	1.3	+ 30%
Washington	545,032	1.7	+ 70%	1.1	+ 10%	1.4	+ 40%
Baltimore	528,376	1.4	+ 40%	1.8	+ 80%	1.6	+ 60%
Minneapolis-St. Paul	533,213	1.1	+ 10%	0.8	- 20%	0.9	- 10%
Buffalo	512,992	2.1	+ 110%	1.2	+ 20%	1.6	+ 60%
Cincinnati	387,299	1.5	+ 50%	1.1	+ 10%	1.3	+ 30%
Milwaukee	415,686	1.1	+ 10%	1.0	----	1.1	+ 10%
Kansas City, Mo.	350,934	2.1	+ 110%	0.7	- 30%	1.3	+ 30%
Houston	326,320	1.0	----	1.5	+ 50%	1.3	+ 30%
Seattle	350,896	1.1	+ 10%	1.0	----	1.0	----

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

II 12A Sub. Selected Pairs of Metropolitan Areas

Lung cancer, code numbers:	White Male Population	ISC #162 Ratio to U.S.Total	ISC #162 Comp. to par	ISC #163 Ratio to U.S.Total	ISC #163 Comp. to par	ISC #162 & 163 Ratio to U.S.Total	ISC #162 & 163 Comp. to par
Denver	266,357	1.5	+ 50%	0.6	- 40%	1.0	----
Dallas	256,817	0.9	- 10%	1.3	+ 30%	1.1	+ 10%
Youngstown	246,666	0.9	- 10%	1.2	+ 20%	1.0	----
Albany-Schenectady-Troy	247,113	1.2	+ 20%	1.7	+ 70%	1.5	+ 50%
New Orleans	234,284	1.9	+ 90%	2.0	+ 100%	2.0	+ 100%
San Antonio	233,635	0.7	- 30%	1.3	+ 30%	1.1	+ 10%
Norfolk-Portsmouth	180,017	1.2	+ 20%	2.2	+ 120%	1.8	+ 80%
Akron	189,198	0.8	- 20%	1.1	+ 10%	0.9	- 10%
Tampa-St.Petersburg	169,998	1.1	+ 10%	1.3	+ 30%	1.2	+ 20%
Birmingham	169,967	2.9	+ 190%	0.3	- 70%	1.4	+ 40%
Springfield, Ill.	60,959	1.2	+ 20%	1.7	+ 70%	1.5	+ 50%
Altoona, Pa.	66,854	0.9	- 10%	0.9	- 10%	0.9	- 10%
Greenville, S.C.	66,554	1.1	+ 10%	1.0	----	1.0	----
Columbus, Ga.	62,774	2.5	+ 150%	0.5	- 50%	1.4	+ 40%
Lincoln, Neb.	57,704	0.8	- 20%	0.5	- 50%	0.6	- 40%
Shreveport, La.	53,114	0.6	- 40%	1.8	+ 80%	1.3	+ 30%
Charleston, S.C.	50,266	1.7	+ 70%	1.8	+ 80%	1.7	+ 70%
Augusta, Ga.	54,294	1.0	----	0.6	- 40%	0.8	- 20%
Green Bay, Wis.	48,515	0.2	- 80%	0.4	- 60%	0.4	- 60%
Galveston	44,888	1.1	+ 10%	1.6	+ 60%	1.4	+ 40%

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

II 13

SMOKING AND LUNG CANCER VARY BY COUNTRY

Sidney RUSS, C.B.E., D.Sc., Professor Emeritus of the University of London, discussed the Doll & Hill (1952) (11-d) study in 1954 (17-r).

He said:

> "In view of the fact that smoking is a widespread habit it would be of the greatest interest to compare the death rates from lung cancer in different countries with their smoking experiences....
>
> "The people of the U.S.A. are the largest per person cigarette-smoking people in the world, yet their lung cancer death rate is about the same as that of the people of Switzerland and Denmark, who smoke about one-half of the cigarette quota of Americans..... Surely there must be some other factor at work.
>
> "This is not a matter of academic interest but one of the highest practical importance. If cigarette-smoking is responsible for the majority of deaths from lung cancer, how is it that people in the U.S.A., who smoke about 30% more cigarettes than we do, show a death rate from lung cancer (1950) less than half that of ours?"

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

NATIVES OF ARCTIC REGIONS ESCAPE LUNG CANCER

Otto SCHAEFER, M.D., of the Canadian Department of National Health and Welfare, Edmonton, Alberta, discussed his four years as a Field Officer in the Canadian Arctic in 1959 (2-s, 3-s). He says:

> "If smoking alone causes lung cancer, we should expect to find many cases in Eskimos and Indians, who almost all smoke quite heavily, mostly cigarettes in recent decades. No bronchogenic carcinoma has been found, however, in Northern natives by our x-ray survey teams, now regularly combing the Mackenzie district and the Eastern and Western Arctic, or in the Charles Camsell Hospital and Mountain Sanatorium.
>
> "While lung cancer has been found in Southern Indians, it is not known to exist in Northern Indians who had not yet any occasion to inhale much air polluted by car exhausts and industrial fumes. I feel therefore inclined to suspect the latter factors as potential carcinogens.
>
> "Neoplastic diseases do occur, but they are less common and of different type-prevalence than in whites."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

II 15

LUNG CANCER VARIES WITH ECONOMIC CLASS

Matthew TABACK, Sc.D., Director of the Statistics Section, and Todd M. FRAZIER, A.B., Director of the Bureau of Statistics, of the Baltimore (Md.) City Health Department, discussed lung cancer and social class in 1955 (1-t). Quotes from their paper follow:

> "The nature of the presently available evidence on the association of smoking and lung cancer has been discussed. There is no doubt that there is an easily proven association between excessive cigarette smoking and a risk of lung cancer. The difficulty seems to arise from the fact that many people misinterpret an association between two factors to be that one factor causes the other, something very much more difficult to prove....
>
> "In studies we have recently carried on utilizing the vital statistics of Baltimore City, the lung cancer mortality for the age group 45-64 years is found to vary consistently and inversely with socioeconomic class. Thus the lung cancer mortality for this age group, both sexes included, is approximately twice as great in the lowest socioeconomic fifth of the population as is found in the highest socioeconomic fifth. Similar type of information has recently been reported in the Statistical Bulletin (Vol. 35, No. 10, 1954) of the Metropolitan Life Insurance Company (43-m), with the conclusion that 'there is an association between respiratory cancer and factors related to environment, occupation, and social class.'"

2015037909

Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

For further references to geographical differences in lung cancer mortality see 3-a, 40-b, 26-c, 39-h, 3-l, 13-m, 14-m, 6-r, 35-s, 36-s, 37-s

For further references to urban-rural factors see 11-c, 23-c, 1-d, 7-g, 8-g, 9-g, 11-g, 17-g, 23-g, 1-h, 39-h, 33-h, 34-h, 35-h, 44-h, 16-k, 2-l, 35-l, 14-p, 16-s

For further references to socioeconomic differences in lung cancer mortality see 23-c, 1-d, 14-g, 24-h, 16-k, 14-k, 13-m, 14-m, 3-o, 47-p, 21-r

For further references to sex differences in lung cancer incidence see 14-b, 26-b, 41-b, 19-c, 23-c, 23-f, 13-f, 14-g, 17-g, 24-h, 32-h, 42-h, 16-k, 3-k, 4-k, 5-m, 10-m, 19-m, 49-m, 13-p, 25-r, 37-s, 15-w

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III-A

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III. HOW MUCH LUNG CANCER IS THERE?

One of the hard truths of epidemiology is that a "fact" is not always a fact--and does not always mean what it seems to mean. It is, for example, a "fact" that in 1958 the death rate from all major respiratory diseases--including bronchitis, pneumonia, influenza, respiratory cancer and tuberculosis--was only one-seventh the death rate in 1900. It is, similarly, a "fact" that recorded lung cancer mortality alone of these diseases has increased, while all other respiratory categories have declined.

These are "facts." But are they real, and are they true or partly true? The answers are still being weighed in scientific studies, some excerpts of which follow. These show that there is evidence that:

1. Some unknown proportion of deaths listed in the past as due to cardiovascular disease, tuberculosis, chronic bronchitis or other conditions really were "missed" cases of lung cancer.

2. As diagnostic accuracy increased with improved methods, equipment, and training, there were fewer "lost" cases of lung cancer mortality and fewer "false" attributions of death to other conditions, resulting in greater numbers of lung cancer deaths being recorded.

3. The increasing number of those who survive severe or chronic attacks of other respiratory diseases in younger years has increased the pool of persons especially susceptible to lung cancer as they enter the older age-groups.

Hence, there is general agreement that the sharp rise in numbers of lung cancer deaths reported in recent years is to a greater or lesser degree "apparent" and not "real," but there is disagreement over estimates as to what extent this is so. No one really knows. Furthermore, some find that underreporting of lung cancer deaths in the past has been succeeded by overreporting today. In this uncertainty--which is by no means restricted to lung cancer mortality figures--it is difficult to measure changes, let alone to assign causes.

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These problems will be illustrated by excerpts from studies dealing with:

A. Under-reporting of lung cancer in the past

B. Errors in mortality data of various types

C. Problems in cigarette-cancer statistical studies.

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A. UNDER-REPORTING OF LUNG CANCER IN THE PAST

Soon after 1900, lung specialists began drawing attention to the neglect of lung cancer by physicians, pathologists, and medical authorities in general. Searching out cases recorded by occasional authors and in hospital records, they commented that mortality data was worthless as a gauge of the frequency of lung cancer.

In succeeding years, the accumulation of such writings resulted in two effects: a marked increase in the recording of deaths from this cause, and a series of changes in the "International Lists of Causes of Death" and in the related Manuals governing death recording practices by doctors here and abroad.

Both factors operated to make direct comparisons of mortality data between years -- and especially between decades -- meaningless. The U.S. Census Bureau did not provide a separate place to list deaths from "cancer of the lung and pleura" until 1914, yet the literature attests to numerous deaths from this cause prior to that year at leading medical centers. Deaths certified as due to lung cancer were classed among "cancer, other sites;" countless other cases were classified as another respiratory disease, or as heart disease and a wide variety of other causes, including "senility" and "ill-defined conditions."

There follow excerpts of representative authoritative medical views on this situation over half a century.

Although there has been considerable improvement over the years in correct death recording, inaccuracies still occur. The difficulty of diagnosing lung cancer is one of the principal factors, as the box on the next page, confined to data from representative American studies, shows.

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DEGREE OF ACCURACY IN DIAGNOSING LUNG CANCER BEFORE DEATH (A TABULATION WHICH SHOWS RELATIVE AMOUNT OF UNDER-REPORTING)

Period covered by series of cases	% of total lung cancers accurately diagnosed	Area of survey	Authority for data
1913	11 %	Chicago	C.V. Weller (4-w,5-w)
1917-1924	33.3%	Chicago	Grove & Kramer (21-g)
1918-1920	40 %	New Haven	T. S. Moise (35-m)
1923-1932	38.4%	Chicago	Hruby & Sweany (30-h)
1927-1937	56 %	Cleveland	S. Koletsky (7-k)
1935-1941	57.1%	Texas	E. J. Macdonald (2-m)
1935-1949	39 %	California	S. M. Farber* (3-f)
1945-1955	82 %	Boston	J. M. Budinger (38-b)

* "We have surveyed 1070 cases of bronchogenic carcinoma, morphologically proven, collected from 19 hospitals in California. In 61% of these cases, no positive diagnosis was made prior to autopsy. Compared year by year, it apparently took as long to make a correct diagnosis of the disease in 1949 as it had in 1935."

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PAST NEGLECT OF LUNG CANCER INCIDENCE

I. ADLER, M.D., Professor Emeritus at the New York Polyclinic Hospital, opened a new era in the study of lung cancer in 1912 when his textbook on primary cancer of the lungs and bronchi appeared (2-a). Quotations relate to the neglect of lung cancer:

> "Most textbooks hardly notice lung tumors, and if they give the subject any consideration it is, for the most part, insufficient..... (A few publications) attempt a more comprehensive presentation of this type of tumor, but they seldom get into the hands of the medical public at large, and so it happens that the general practitioner is not in a position to diagnosticate a primary lung tumor as often as might be, and the belief in the extreme rarity of these cases is still maintained.
>
> "To add to these difficulties, even the diagnoses made on the autopsy table are not always reliable.... Another important addition to the difficulties to be contended with lies in the fact that in many countries, as for example our own... the overwhelming great majority of the dead are not subjected to any post-mortem examination, and the death certificates on which burial permits are officially given are often ludicrously insignificant.
>
> "For this reason the United States Census is entirely useless for our purpose. It is... impossible to say... how many persons mentioned as having died from tuberculosis, pneumonia, or kindred diseases, may not really have died from lung tumors....
>
> "There is as yet no known primary cause for malignant growths.... It is more than doubtful whether environment, as some authors maintain, plays any active part in the development of malignant growths."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

FREQUENCY OF LUNG CANCER UNDERRATED IN THE PAST

Carl Vernon WELLER, M.D., of the Department of Pathology, University of Michigan, Ann Arbor, made a study of cases of primary carcinoma of the larger bronchi that were verified by autopsy in 1913 (4-w). His opinions were in part as follows:

> "There has been a growing realization of the fact that bronchial and pulmonary carcinomata are by no means as rare as was once thought, and the developing possibilities of intrathoracic surgery have made their early diagnosis a matter of more than scientific curiosity....
>
> "It is often found impossible to determine even roughly the point of origin of the growth, because of the enormous size of the neoplasm and the widespread involvement of surrounding structures, but there is a large group in which the bronchial origin may be established....
>
> (90 cases are reviewed in capsule form)
>
> "In a few cases an ante mortem diagnosis of bronchial carcinoma is absolutely impossible... On the other hand, diagnosis is often possible, as is shown by the fact that in about ten of the cases listed in this paper the nature of the process was ascertained before necropsy." (11%)

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

LUNG CANCER MISTAKEN FOR OTHER DISEASES

Maurice PACKARD, M.D., Professor of Clinical Medicine at New York Polyclinic Hospital and Medical School, discussed lung cancer problems in 1917 (1-p):

> "The difficulty which is encountered in attempting to establish an early clinical diagnosis of primary cancer is well known to the clinician, and is amply emphasized by many observers. This difficulty is probably due to the similarity between such a cancer especially in its earlier course and many other intrathoracic conditions, such as tuberculosis, unresolved pneumonia, pleurisy with effusion, pulmonary lues, and thoracic aneurysm.
>
> "It is not uncommon even in our present-day knowledge to note in our professional literature, instances where the disease has been entirely overlooked, and the nature of the condition has been revealed only through an autopsy.
>
> "Thus, Swan (51-s) reported the history of six cases who were sent to Colorado with a diagnosis of pulmonary tuberculosis, and the autopsy disclosed the true nature of conditions, all malignant intrathoracic tumefactions. Bromwell (50-b) relates a case of primary sarcoma of the lung proved by autopsy, which was previously demonstrated in the clinic as an advanced case of pulmonary tuberculosis, with cavity formations. Henrici (41-h) speaks of a case shown by autopsy to be a primary cancer of the lung in which the clinical diagnosis was unresolved pneumonia....
>
> "The roentgen rays have considerably furthered the diagnosis of tumors of the lung.... During the last few years intrathoracic surgery... has been materially widened, and we feel that the patient suffering from this dreadful malady should at least be given the opportunity of relief by operation."

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DIFFICULTIES IN DIAGNOSING LUNG CANCER DURING LIFE

Maurice FISHBERG, M.D., and M. STEINBACH, M.D., of the tuberculosis division of the Montefiore Home and Hospital for Chronic Diseases of New York City, in 1921 highlighted the many difficulties encountered in diagnosing lung cancer (9-b):

> "During the past five years.... there appears to have occurred an increase in the absolute, as well as the relative, number of cases of primary malignant neoplasms of the lungs. This increase has, however, been noted mainly by pathologists while making autopsies; most cases had been otherwise diagnosed during life....
>
> "Nearly all our patients, before admission to the Montefiore, were in other hospitals or clinics, where efforts at making a diagnosis had been made. The result was that the 33 patients were referred to us with the following diagnoses: cancer of the lung, 4; pulmonary tuberculosis, 13; pleurisy with effusion or empyema, 7; chronic pneumonia, 2; cardiac disease, 2; neurosthena, 1; abscess of the lung, 2.....
>
> "It seems that malignant growths of the lung are so often missed because it is considered an exceedingly rare disease, and is never thought of when an atypical case of some more common pulmonary disease is examined..... Cells not unlike those of malignant tumors may be found in the sputum expectorated by patients suffering from any disease of the bronchi, lungs, or throat (and).... may deceive the most competent pathologist.... Likewise, examination of the pleural exudate has been of but little value.... Of greater utility has been found radiography in lung tumors, but in many cases it proves misleading or negative."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

CANCER, NOT A SINGLE DISEASE, WAS VIRTUALLY UNKNOWN IN 1900

A comprehensive review of "A half century of effort to control cancer" was presented in 1955 (52-p, 53-p, 54-p) by George T. PACK, M.D., FACS, Associate Clinical Professor of Surgery, Cornell University Medical College, and Irving M. ARIEL, M.D., FACS, Assistant Professor of Surgery, New York Medical College, of New York City. Following are selections from their discussion of the general characteristics of cancer, and the historically recent development of interest in the disease.

> "The discovery of hundreds of chemically dissimilar agents capable of carcinogenesis and the bizarre and unpredictable reactions which occurred upon the application or ingestion of carcinogenic agents demonstrated that the metabolic status of the host played a significant role....
>
> "The discoveries that certain pure bred animals spontaneously develop cancer, the identification of viruses which are carcinogenic (Shope papilloma), the identification of the extrachromosomal mouse milk factor of Bittner and its bizarre epidemiology, the identification of numerous chemical and other carcinogens, and the effects of hormones and dietary supplements in enhancing or retarding the mechanism of these reactions indicate the complexities of carcinogenesis....
>
> "Any of the myriad combinations (of numerous factors)... can produce cancer. Any cell (or group of cells) in the multicellular animal, under proper stimulation and environmental conditions, can theoretically develop cancer. Etiologically, cancer is a group of diseases rather than a single disease entity....
>
> "Although most of the information resulting from animal cancer research is not directly transferable for the understanding of human cancer, certain generalizations are permitted.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

"1. Cancer in the human being is not a single disease; it represents a cellular end result evoked by many different forms of stimuli....

"2. Heredity, which plays a major role in certain animal cancer experimentation, plays but a minor role in human cancer....

"3. Certain species or strains of animals will react to cancer with varied reactions....

"4. In the past cancer was believed to be purely an autonomous growth..... This has been shown to be untrue in certain instances. The vivid evidence from cancer research has indicated that certain neoplasms, especially of the prostate and breast, are under hormonal controls....

"Cancer was the ninth most frequent cause of death in 1900; hence it is not surprising that efforts to control infectious diseases dominated medical thought. There was practically no cancer research; the occasional individual who manifested an interest in the disease was regarded with suspicion. Many hospitals refused admission to patients with cancer, considering the disease hopeless. There was only one cancer hospital, no cancer clinics, and no detection centers. No education for the public existed, and the only exposure the physician had to the disease was in the morgue or the pathology laboratory, or as the occasional assistant of a bold surgeon.

"Vital statistics were non-existent. X-rays had been discovered only 5 years before and radium but 2 years previously.... Neoplasms arising in the lung, esophagus, pancreas, liver, and central nervous system were not considered in the surgical domain....

Respiratory system

"Cancer of this system shows the largest relative increase in mortality rates of all the major systems... There is agreement that many more lung cancers are now being correctly diagnosed, but not nearly enough to be apparently benefited by treatment. The larynx is the other major site of cancer of the respiratory system, but the mortality has increased less rapidly than that from cancer of the lung...."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

DIAGNOSTIC ERRORS IN CANCER REPORTED

H. Gideon WELLS, M.D., Department of Pathology, University of Chicago, and the Otho S. A. Sprague Memorial Institute, in 1927 discussed "Cancer Statistics as they Appear to a Pathologist" (8-w & 9-w), based on extensive necropsy findings. He said:

> "In these 100 necropsies, the diagnosis of malignant disease has been made, either before or after death, in 27 cases. In just 11 of these cases, the clinical diagnosis made before death agreed completely with the necropsy observations.... Is it strange that many pathologists.... are skeptical of cancer statistics?....
>
> "A few years ago (1923) (7-w) I analyzed a series of 3,712 necropsies from my own records and from the Cook County Hospital, which includes 545 cases of malignant neoplasms. Of these, 367 were recognized as cases of malignant disease during life, irrespective of whether the site or character of the neoplasm was correctly diagnosed; 178, or 32.7%, were not recognized as malignant disease during life, and, in addition, there were 33 cases in which cancer was diagnosed but in which it was not found at the necropsy....
>
> "Such a high ratio of incorrect diagnoses in a great hospital might seem to be evidence of something wrong with the hospital, but we find that other institutions dealing with a similar class of cases, in which most of the cancers coming to necropsy are of the internal organs, exhibit not dissimilar figures.....
>
> "To one who is familiar with the way in which death certificates are prepared outside the hospitals, there seems to be a possibility that here too a very large diagnostic error also obtains, and this is especially true with the death certificates for the aged, among whom internal cancer is a very common cause of death.... Knowing that the death is from natural causes, the local physician is commonly satisfied to certify it as one of the common maladies of the aged, such as pneumonia, nephritis or heart disease..

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"The main point, however, is not whether the errors disclosed by post-mortem examinations are greater or less abundant than the diagnostic errors that are buried with the patients not submitted to necropsy. The vital fact is that we do not know and cannot find out how great the error in the vital statistics may be....

"Obviously, every person saved from death in youth becomes a potential victim of cancer in later years, and consequently every improvement in public health leads to an increased cancer mortality.... A high crude cancer death rate is evidence of a good state of public health, being high in direct proportion to the degree of control of preventable diseases... Likewise, every forward step in diagnosis, hospitalization and medical observations adds to the number of recorded cases of cancer....

"Another important factor in the increasing cancer rate is the improved recording of vital statistics. In many countries the older rates are based on death records, a large proportion of which were filed by non-medical persons, in some places the parish priest, in others the undertaker, often by friends and relatives.... A large error in earlier statistics also lay in the recording of deaths of old people as resulting from 'senility,' 'old age,' and 'causes unknown.' The refusal of authorities during recent years to accept this sort of diagnosis has undoubtedly been responsible for transferring many cases to the list of deaths from cancer. The trouble is that there is no possible way to learn how many such transferred cases there are in any set of vital statistics."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

CHANGES IN DEATH CERTIFICATE FASHIONS AFFECT COMPARABILITY

Major GREENWOOD, Fellow of the Royal Society, England, studied the purposes and nature of medical statistics in 1948 (18-g):

> "All students of official statistics who attend lectures are warned to read footnotes and introductions. That warning should be particularly heeded by students of medical statistics. Change of fashion in certification due to increasing knowledge may affect comparability....
>
> "One should never believe that a disease is becoming more, or less, deadly until all other explanations have been excluded. A particularly important break in continuity occurred in 1940....
>
> "It is inevitable that, from a short study such as this, much which is important must be omitted, but enough may have been said to help the reader to find his way into the literature. Most statistics can be used and are used for propaganda; hardly any are used more frequently for this purpose than medical statistics, so the student is once again urged to scrutinize the medical-statistical arguments of very important persons with great care and to verify the statistics used. Only very foolish propagandists misquote figures given in official tables, but they may have overlooked footnotes or introductory comments."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

B. ERRORS IN MORTALITY DATA OF VARIOUS TYPES

Although death recording practices are far from perfect today, they are nonetheless an improvement over the past. However, officials concerned with vital statistics themselves have expressed dissatisfaction with the lack of comparability of mortality data, which they attribute to several factors. These include: decennial revisions of the International List of Causes of Death; changes in the official Manuals governing death recording practices; "diagnostic fads" reflecting changes in reporting practice or popular interest (1-v); changes in composition of the so-called "Death Registration States" in this country (2-v); changes in reporting that introduce fluctuating variables in death certification (3-v); and combinations of these various factors.

Thus, no one is at all sure that the lung cancer death rate per 100,000 has risen anywhere near the extent that one would assume from consulting the data showing an increase in numbers. The mere increase in population of older age groups, where the incidence of lung cancer is higher, has resulted in a substantial increase in the number of lung cancer cases.

Other influencing factors are the availability of more and better hospital facilities, improved training of doctors and pathologists, and increase in type and quality of diagnostic techniques, described in the box following. These and related matters are discussed in this section.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

Diagnostic Improvements

In virtually every decade of the present century some new or highly improved technique has been added to the arsenal of diagnostic means available to the lung cancer specialist. There are, of course, other diagnostic aids (omitted for purposes of clarity) which also have improved with the years or have been introduced in a recent past. The point is that as diagnostic means increase in number and refinement, the greater the number of lung cancers found.

Since a new technique is not adopted everywhere at the same time, the dates given below indicate the approximate span of years during which a method came into "general" use. It must be further noted that not every hospital has on its staff trained specialists to carry out all of the diagnostic procedures listed; cytology, in particular, is performed at relatively few institutions.

Lung cancers are still being "missed" -- but less so than twenty, forty and sixty years ago.

Method	Improvements	Introduced	Status	References
X-rays		1900-05	In use	(11-o)
	Bronchography	1925-30	Obsolescent	(28-f, 22-m, 72-s)
	Tomography	1935-40	In use	(70-b)
	Angiography	1940-45	In use	(37-r)
Bronchoscopy		1900-10	In use	(71-b, 6-j, 7-j, 24-k)
Thorascopy		1910-15	*Obsolete	(14-f, 8-j)
Cytology, sputum		1935-40	In use	(28-d, 50-p)
--- aspirative		1947-52	In use	(24-a, 39-c, 55-h, 51-p)
Biopsy, needle		1935-40	*Obsolete	(11-h, 71-s, 9-v)
--- bronchoscopic		1946-50	In use	(40-c, 12-n)

*Thorascopy and needle biopsy have been almost entirely abandoned owing to risk of spreading cancer cells.

For general discussions of lung cancer diagnosis, see 19-b, 14-f, 8-h, 22-m, 52-p, 53-p, 54-p, 14-r.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

DIAGNOSTIC IMPROVEMENTS IN LUNG CANCER

Edward A. LEW, Actuary and Statistician of the Metropolitan Life Insurance Company, New York City, analyzed mortality data on respiratory cancer in 1955 (12-1):

> "There is considerable evidence that developments leading to more careful and more frequent diagnostic study of patients as well as improvements in diagnostic techniques have played a very important part in the recorded rise of respiratory cancer death rates. This evidence cannot, however, be translated into estimates of the proportions of deaths currently reported as due to respiratory cancer which 25 years ago would have been reported under cancer of other sites or as due to other diseases.
>
> "The more significant pieces of evidence are:
>
> "1. As a result of more and better instruction in diagnosis at both the undergraduate and graduate levels, there has been a great increase in the number of physicians with good training in diagnosis. The number of specialists in radiology and bronchoscopy has also increased markedly. Furthermore, the publicity given in the medical and lay press to the sharp rise in respiratory cancer has of itself led to greater awareness of this disease and thus to more frequent search for it.
>
> "2. The facilities available for diagnosis of respiratory cancer and their use have likewise multiplied....
>
> "3. The development of better diagnostic methods... and the more frequent use of radical surgery have uncovered many cases of respiratory cancer which would have been missed in earlier years....
>
> "4. The fact that the magnitude of the respiratory cancer death rates is clearly associated with the quantity and quality of medical facilities, and that during the 1940's respiratory cancer death rates increased most in states with low death rates and relatively low ratios of physicians to population, also supports the view that much of the increase in respiratory cancer was the result of improved diagnosis and more complete case finding.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

"5. The marked increase during the 1940's in the reported respiratory death rates from respiratory cancer among non-white lives can also be attributed largely to improved detection and better reporting....

"6. The sharp declines in the mortality from tuberculosis, pneumonia, and other respiratory diseases, such as chronic bronchitis, have probably resulted in the detection of respiratory cancer cases which formerly would have been reported as deaths from these diseases....

"7. An increase in the proportion of cases where the respiratory system is reported as the sole or primary site rather than as the secondary site may be another factor in the recorded rise in respiratory cancer death rates...."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

III-B 5

ANALYSIS OF DIAGNOSTIC ERROR EFFECT ON LUNG CANCER MORTALITY

Alexander G. GILLIAM, M.D., Biometry and Epidemiology Branch, National Cancer Institute, of Bethesda, Md., has several times reviewed the statistical data on lung cancer mortality. In 1955 he discussed the possible effects of wrongly certifying lung cancer deaths as some other respiratory diseases (9-g):

> "It has been shown that all of the increase in mortality attributed to cancer of the lung since 1914 in United States white males and females cannot be accounted for by erroneous death certification to other respiratory diseases, without unreasonable assumptions of age and sex differences in diagnostic error. This fact strengthens the belief that part of the recorded increase in cancer of the lung is real. It is also demonstrated, however, that numerically small diagnostic errors in these diseases in both males and females 35 or more years of age can account theoretically for a substantial portion of the recorded increase. Thus, if as few as 2 per cent of deaths in persons 35 years of age and older that were attributed to other respiratory diseases were in fact due to cancer of the lung, the recorded increase in white males since 1914 would be 4-fold instead of 26-fold and the 7-fold increase in females would be reduced to 30 per cent. The ratio of increase would be further reduced on the more realistic assumption of greater diagnostic error in the earlier than in the later years considered.
>
> "A brief review of the literature provides evidence that diagnostic errors have occurred and that an error of 2 per cent does not appear unreasonable. It is to be hoped that the records of large hospitals having active necropsy services will be reviewed to provide more reliable estimates of diagnostic error, due regard being given to the age and sex not only of the lung-cancer but of all the patients, as well as to their grouping into several time periods. Evidence has been presented that strengthens the belief that liability to cancer of the lung has increased, and is still increasing, but that the magnitude of increase is nowhere near as great as recorded mortality suggests."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

ANALYSIS OF LUNG CANCER MORTALITY DATA

Eleanor J. MACDONALD, Professor of Biostatistics at Postgraduate School of Medicine, the University of Texas, and Epidemiologist at the University of Texas M.D. Anderson Hospital and Tumor Institute, in a 1955 paper on "Epidemiology of Cancer" (2-m) said:

> "Most of what is known of the frequency of cancer has been gathered from death certificates furnished by physicians or government officials.... Since the increase in cancer is based on the death certificates, studies from time to time are made to check the current status of their accuracy. Several years ago the author studied the death records for a given year in Massachusetts to find out if the data upon which extensive biometrical methods were being used, were basically accurate enough to warrant this expenditure of effort. Approximately 15,000 individuals were interviewed to verify the data.... (1-m)
>
> "This study showed a large error in exact location of cancer. As to the fact of cancer, reporting was 89% correct. Eleven per cent were recognized only at autopsy and not suspected in life. Five per cent were erroneously called cancer. As to site of cancer, agreement was only 75% correct with the greatest discrepancy occurring in liver, digestive tract, respiratory tract and male genito-urinary tract, due to the practice of certifying a death record as cancer of its metastatic rather than its original site....
>
> "The effect of intense publicity in drives for funds for cancer, poliomyelitis and heart disease is reflected in death certification in the United States. This is measurable because such increases are spasmodic in nature and tend to return to normal proportions when the publicity stops or the emphasis is on other sides of the question beside proportionate mortality....

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

"Until 1944, then, the gradual increase in cancer deaths ran a parallel course with the gradual increase in the population. Since then it has reflected the success of the current publicity on cancer....

"Since the biggest recorded increase in cancer was in cancer of the respiratory system and since the second biggest drop in deaths occurred in other respiratory disease, breakdownswithin each of these categories were made. Within the other respiratory disease deaths, the big reductions were in the pneumonias and influenzas, probably the reflection of the general use of antibiotics.

"The use of antibiotics has another side effect, the volume of which is not fully known. It has separated some respiratory cancer from conditions hitherto considered to be chronic respiratory infectious diseases, since the former would not respond to antibiotics and the infections in most instances would.

"Such a means of differential diagnosis plus Papanicolaou's testing of sputum and other diagnostic advances would account for some of the apparent numerical increase in respiratory cancer, which would actually mark an improvement in diagnostic determinations of lung cancer present all the time rather than an actual increase."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

III-B 8

DOUBTS HELD ON VITAL STATISTICS

Hugo MUENCH, M.D., Dr.P.H., FAPHA, Professor of Biostatistics, Harvard School of Public Health, in 1959 wrote on the subject of "Figures, fancies and fancy figures" (40-m):

> "... There is a good deal of natural magic left in our attitude toward numbers in tables of vital statistics, as though such figures had an independent existence and truth value of their own, quite aside from the manner of their arrival in the cells of the table. We need not fool ourselves. We may be perfectly aware of the fact that the original data are highly dubious, that there are possible errors along the way, and that our final classification may have had to be a bit arbitrary. Yet, once a datum has taken its place as a cold figure printed in the cell of a table, we unconsciously tend to regard it as the representative of a truth beyond the influences of an erring world....
>
> "The chain connecting the occurrence of an event with its appearance in a table has three major links: recognition, reporting, and classification. The confidence we can place in the tabulated figure evidently depends on the confidence we can have in each and all of these, and this must vary greatly under different conditions. If we as statisticians are to act as apostles of truth, we must at least try to evaluate the level of this confidence. Our main difficulty is that so much of our information is gained by means of what amounts to questionnaires, even if they are questionnaires which the respondent is under some pressure to return....
>
> "Where is our difficulty? Mainly, it seems, in our uncritical demand for more information than is properly available.... We seem to be convinced that dubious information, if collected on the broadest possible base, will attain to reliability. This just is not true!...."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

VIEWS ON THE RECORDED RISE IN LUNG CANCER

D. W. SMITHERS, M.D., FRCP, D.M.R., Director of the Radiotherapy Department, Royal Cancer Hospital, and Radiotherapist, Brompton Hospital for Diseases of the Chest, London, England, in 1953 wrote on "Facts and fancies about cancer of the lung" (26-s):

> "The startling rise in the recorded death rate from cancer of the lung and the implication of one of our favorite indulgences as chief culprit have suddenly made this a matter of public interest....
>
> "Much of the recorded rise can be accounted for. The number of persons living in England and Wales has gone up by $7\frac{1}{2}$ millions in the past 40 years, and the age distribution has so changed that 21 persons in every 100 alive today are over 55 years of age, while only 12 persons in every 100 were over 55 then.
>
> "The number of doctors resident in this country has also increased in this period from 25,000 to 48,000, which is a change from about 1400 persons per doctor to about 900.... Even today, however, the accuracy of the diagnosis of bronchial carcinoma in the country as a whole and the reliability of death certification from this cause must still be under grave suspicion....
>
> "From the large pool of patients dying with symptoms common to many chronic lung and heart disorders, an increasing number are being labelled 'lung cancer' on a decreasing post-mortem examination rate for the total, despite a rising post-mortem rate for those dying in many hospitals. There is a wide variation in the degree of uncertainty with which this diagnosis is made.
>
> "Death from respiratory disorders is relatively common, from lung cancer comparatively rare. Without taking any account of patients dying from cardiac disease with similar symptoms there would still have been little difficulty in losing our entire present lung cancer death rate in the general death rate from respiratory disease in the past if these cases were really there to lose....
>
> "As a profession which speaks so much and so rightly of the need to allay the cancer fear we should beware of putting extravagant accounts of rising cancer death rates and their causes before the public, especially when neither the magnitude of the one nor the degree or responsibility of the other has yet been fully established."

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LUNG CANCER MISDIAGNOSED

Jane M. FULLERTON, M.D., of St. Olave's Hospital, in London, England, recited chapter and verse on 22 cases of lung cancer recognized only at autopsy (showing the G. P.'s referral, the x-ray reports, and the hospital diagnosis in each instance) in 1956 (17-f). She said:

> "The increase of deaths from cancer of the lung from 2,286 in 1931 to 17,271 last year, as quoted by the Minister of Health, looks very alarming, but little is said, when considering these figures, of the great improvements in the hospital services and diagnosis contributing to this increase. Apart from widespread x-ray facilities, skill in bronchoscopy, etc., many hospitals have now a pathological service which did not exist in 1931, and indeed not until the advent of the Health Service. This latter has meant, in many cases, an increase in the post-mortem diagnosis of carcinoma of the lung which has been unsuspected clinically.
>
> "I have been interested in the arguments for and against the 'increase' of carcinoma of the lung, and a few years ago analyzed the figures in St. Olave's Hospital for the three years prior to my appointment and the setting up of a group laboratory in this area, and the three years after, with the following results: -- January, 1947, to December, 1949: total number of deaths, 989; total number of necropsies, 348 = 36.1% of deaths; carcinoma of bronchus diagnosed clinically and at necropsy, 37 cases.
>
> "In the following three years I was able to ascertain prior to necropsy the clinical diagnosis with the following results: total number of deaths, 1,218; total number of necropsies, 753 = 61.7% of deaths; carcinoma of lung suspected before death found at necropsy, 22 cases; total number of cases of carcinoma of lung, 59...
>
> "To me the fact that in three years in this hospital alone the number of cases of carcinoma of the lung was increased by 22 purely on post-mortem evidence is interesting, and I feel that throughout the country many of my colleagues must have had similar experience. If so, perhaps the increase in deaths from lung cancer is not so great as the figures would have us believe."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

III-B 11

SELECTION
AND OTHER
FORMS OF BIAS
IN BIOSTATISTICS

George L. SAIGER, M.D., Associate Professor of Epidemiology and Consultant in Medical Research, Columbia University School of Public Health and Administrative Medicine, New York City, in 1960 wrote on "Errors of medical studies" (70-s), which he believes reflect hasty efforts to keep up with voluminous research into etiology and therapy.

> "Thus, it has become exceedingly important that investigators exercise more care in planning and executing their studies, in analyzing the results and drawing conclusions from them, and in reporting those results and conclusions in the literature....
>
> "The researcher's ability to make an inference is not as limited as his ability to measure the degree of confidence to be placed in that inference. In order to gauge the uncertainty of an inference, he cannot exercise any prejudice or bias when he selects a sample. To select without bias is to allow every subject an equal and independent change of being included in a sample. This is known as random sampling; the word 'random' refers to the method by which the sample is chosen and not to the sample itself....
>
> "Selection -- Vaccination may be thought of as an index of a well-informed parent's desire to safeguard his child's health. Other protective measures such as good nutrition and personal hygiene may make vaccination appear beneficial when it really is not. This type of sampling bias is known as selection. Selection need not imply that the results of a study are biased. If factors identified with selection are unimportant, the direction in which a study points may not be biased even though the sampling procedure is. It nevertheless is the responsibility of the investigator to show that such factors are unimportant.
>
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>
> "An element of selection also may be present in studies on smoking and lung cancer, and the fact that they occasionally bear the label 'prospective' does not make them immune to this sort of bias. For example, it is conceivable that a person's preference for smoking is determined to a large extent by his health habits in general.

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"These habits also may govern his susceptibility to respiratory illness, and respiratory illness in turn may predispose a person to cancer. Indeed, there is evidence to suggest that pulmonary infections are rather important in the etiology of lung cancer, decidedly important enough to be investigated more thoroughly....

"As of the moment, the best that can be said is that lung cancer may have a rather diverse etiology. Several factors have been implicated including heredity, inflammatory processes, and air pollution, of which tobacco smoke is a concentrated form. (In a sense, to accept the theory on air pollution is to accept it on tobacco as well. The evidence is circumstantial in either case.)

"In consideration of criticisms raised against studies on cause and effect, it seems reasonable to conclude that the probability that a substance identified with that characteristic will cause the disease unless it is known unequivocally that the substance is capable of producing the disease in at least one member of the species. There is an inherent contradiction in the statement that a person's risk of developing lung cancer will be reduced by the elimination of tobacco.

"There is room for bias in any study in which interviewers select the persons whom they are to study. This has been the case in a recent follow-up study on the relationship of smoking to death rates for various causes (6-h)....

"Statistics tend to show that in addition to an increase in the recorded death rate for lung cancer in the past several decades, there has also been an increase in the per capita consumption of cigarettes. Although we may be sensitized to the fact that this association may have no real bearing on cause and effect, what we are less able to appreciate is that the strength of the association itself can be reduced by correcting or allowing for such factors as an aging population and an improved system of reporting, selecting, and classifying causes of death and that whatever remains could be due at least in part to improved diagnostic acumen, methods, and facilities and to an increased awareness of cancer on the part of the medical profession and the public."

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LUNG CANCER DIAGNOSIS IS STILL PROBLEM

William O. UMIKER, M.D., of The Departments of Pathology, Veterans Administration Hospital and the University of Michigan Medical School, at Ann Arbor, in 1957 (4-u) reviewed false positive reports in the cytologic diagnosis of lung cancer.

> "The value of exfoliative cytology in the diagnosis of lung cancer has been established, but the elimination of false positive reports has not been accomplished.... Iversen (1953) (1-i), who reviewed the literature and summarized the cytologic and clinical findings in 47 false positive cases, found false positive smears most frequently in patients with bronchiectasis, pneumonia or lung abscess. Foot (1955) (30-f) also reported false positive smears due to bronchiectasis or pneumonia. Atypical squamous cells, large ciliated columnar cells, and 'Pap' cells were responsible for most of his false positive results. Farber, Benioff, Frost, Rosenthal and Tobias (1948) (29-f) reported that histiocytes may also simulate cancer cells.
>
> "This paper is a presentation of a study of benign atypical cells which simulate malignant cells in sputum or bronchial secretions.... There were four types of cells which simulated cancer cells: atypical squamous cells, 'Pap' (Papanicolaou) cells, large columnar cells and large basophilic 'smudge' cells of undetermined nature....
>
> "Atypical squamous cells were encountered in five patients, including a patient whose false positive report resulted from chronic organizing pneumonia and pulmonary infarction with atypical squamous metaplasia of bronchioles. One other patient in this group has a pulmonary infarct. The clinical diagnosis in two cases was chronic bronchitis. The fifth patient had severe bronchiectasis...."
>
> Discussing columnar cells, the author says it is debatable whether malignant respiratory cells ever have cilia, but for practical purposes any cells with cilia should be regarded as benign.

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III-C

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C. ANALYSES OF THE CIGARETTE-LUNG CANCER STATISTICAL STUDIES

The theory that cigarette smoking is a cause of lung cancer derives in large part from three studies: one of 187,783 American men aged 50 to 69, undertaken by Hammond & Horn for the American Cancer Society (6-9-h); another of 40,701 physicians by Doll & Hill for the British Medical Research Council (12-13-d); and the third of 198,926 U.S. war veterans with Government insurance (21-d). These were "prospective" studies: that is, smoking data was collected in advance of death. When a person in the groups surveyed died, his cause of death was recorded and classified according to ascertained smoking habits. Only a relatively small number in each group had died when reports were made. With some differences (not relevant in this connection) all three studies reported a larger proportion of "heavy" smokers than light smokers and non-smokers among those dying of all causes, of lung cancer, of heart disease, and of a large number of other conditions. From these data, a number of conclusions and assumptions have been advanced covering the effect of smoking.

Various analyses have been made of these studies, only a few of which are summarized here. While some reviewers accept the data and the conclusions, others have levelled challenges at many points: the scarcity of the data about many other variables in environment, socioeconomic status, occupation, previous medical history, and habits that it might be desirable to know; the presence of various forms of statistical bias noted by specialists in the field of epidemiology; and criticism of assumptions that the findings show a cause and effect relationship.

The following excerpts cite some of the questions that have been raised as to the specificity of tobacco use in lung cancer and other diseases named in the three surveys, the aberrations in the data when the decedents had mingled the use of pipes and cigars with cigarette smoking, the seemingly "protective" effect of inhalation in the only one of these surveys where it was recorded, and other factors.

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SMOKING DOUBTED AS A CAUSE OF LUNG CANCER

Joseph BERKSON, M.D., Chief of the Section of Biometry and Medical Statistics of the Mayo Clinic, Rochester, Minn., and member of the Committee on Research and Statistics of the American Cancer Society, in 1960 (68-b) published the latest in several analyses of the statistical studies of smoking and lung cancer by Hammond & Horn (6-h, 7-h, 9-h), Doll & Hill (10-d, 11-d, 12-d, 13-d), and Dorn (21-d):

> "Without false modesty, and quite frankly, I am going to reveal to you that, really, I do not know the cause of cancer. Moreover, I am going to say, with only slight fear of contradiction, that no one else does either.
>
> "Now, when the cause of a disease is not known, frequently it gets attributed to practices that are not approved, like the use of alcohol, perhaps, or like smoking....
>
> "Does cigarette smoking cause cancer of the lung? I say cigarette smoking specifically, because the recent statistical studies that have occasioned the present discussion pretty much absolve cigar and pipe smoking, and this, incidentally, is in itself curious. Well, I can only express an opinion, but it is based on a fairly careful examination of the accumulated evidence. In my own opinion, all available relevant facts considered, it seems very doubtful that smoking causes cancer of the lung....
>
> "The cause of cancer is fundamentally not a statistical question, but a biologic one. Statistics, if critically and carefully used, can provide useful 'leads,' but the definitive investigations must come from the biologic sciences, pathology, pharmacology, chemistry and so forth. All of them together must be brought to bear on the problem, if we are to answer the specific question at hand, and the many other questions that are involved. For we will not really know whether smoking causes cancer, till we know at least something in a precise way about <u>how</u> it causes cancer....

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"So far as clinical evidence is concerned, I should not fail to mention here that it had been early noted by others that the notion of smoking as a cause of cancer was incongruous with clinical experience. For smoking was supposed to be specifically the cause of the epidermoid, rather than the adeno type of cancer, and long-time smokers who have their fingers stained heavily with concentrated extracts from cigarettes do not develop epidermoid cancer.... It is common knowledge that cancer does not develop.... in smoker's sore throat, or in smoker's bronchitis, and that direct experiments attempting to produce bronchogenic cancer by smoking are all negative in results....

"Now, about these statistics.... The definitive finding in these prospective studies really is not that there is an association between smoking and cancer of the lung, but that there is a statistical association between smoking and death from all causes generally, of which cancer of the lung is only a small part.... If we take the higher death rate from cancer of the lung among the smokers to evidence that smoking causes such cancer, then we must also accept that smoking causes cancer of the stomach, of the bladder, of the prostate, for all of which the death rates are higher among the smokers.... We have 'proved too much,' and a scientist would be inclined to say, 'There must be something wrong with this method of investigation.'

"How shall these unexpected findings be explained? I have suggested a number of explanations for consideration and for testing by appropriate investigations, of which I shall here mention only the two most simple. The first is that the associations are a spurious statistical phenomenon, related to the vagaries of the data as obtained in these statistical studies.... The second... is that the statistical association of smoking with larger death rates in general has a constitutional basis.... There are now a considerable number of independent studies that support the premise of this theory that smokers as a class are of a different general constitutional type than non-smokers."

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III-C 3a

GERMAN SMOKING-LUNG CANCER STUDY DENIES CAUSAL RELATIONSHIP

Ernest DORMANNS, M.D., Professor of Pathology, Municipal Hospitals of Solingen, Germany, reviewed all available German data in a study of a possible association between smoking and lung cancer in 1954 (18-d). He reported as follows:

> "1. Autopsy analysis in Munich for two periods -- 1901-1911 and 1922-1931 -- showed that the incidence of lung cancer increased 800 to 900 per cent for both men and women. If this rise were due to tobacco consumption -- assuming that any carcinogens in tobacco require about 20 years to take effect -- then there should have been a sharp rise in tobacco consumption beginning about 1902. This was not the case.
>
> "2. Relatives of autopsy-proved lung cancer victims in Solingen were interviewed to determine the smoking habits of these patients. The investigation showed that two-thirds of these lung cancer victims were cigar and pipe smokers and had never smoked cigarettes during their entire life. Only 33.3 per cent of these lung cancer victims were cigarette smokers.
>
> "3. As noted previously, there was an 800 to 900 per cent increase in lung cancer in Munich in 1922-31 compared to 1901-11. But statistics on cigarette consumption in Germany showed that the average cigarette consumption did not increase markedly during this period and did not, in fact, rise substantially until after World War I (then reaching a level of 322 per year, or less than one cigarette per day, on the average).
>
> "Therefore 'a causal relation between the smoking of cigarettes and the increase in the incidence of carcinoma of the lungs may be denied with a high degree of probability for all of Germany.'"

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INHALING SMOKE AND LUNG CANCER

Sir Ronald A. FISHER, Sc.D., F.R.S., whose pioneer work in the field of medical statistics for the past forty years has earned the title, "Father of Modern Statistics," included a new discussion of "Inhaling" in a booklet published in the summer of 1959 (10-f). Excerpts from this analysis follow:

> "When several years ago, it appeared that a verifiable association could be established between smoking and cancer of the lung, and before there was any reason to doubt the simple theory that the products of combustion could so act on the surface of the bronchus as to induce the growth of a cancer, it was natural to seek the powerful confirmation of this theory which would be obtained if those practicing inhalation of cigarette smoke appeared with much higher frequency among the cancer patients than among those suffering from other conditions.
>
> "The failure of Hill & Doll's retrospective inquiry to supply such corroboration took these workers by surprise, and at first they could scarcely believe that the question had been understood. The investigators who actually questioned the patients, however, seem to have had no doubt of this; and the statisticians had the embarrassing choice between frankly avowing that one striking and unexpected result of their inquiry was clearly contrary to the expectations of the theory they advocated, or to take the timid and unsatisfactory course of saying as little about it as possible. It has taken some years, therefore, to elicit the tables below,

TABLE I

Maximum daily cigarettes

		1-4		5-14		15-24		25-49		49	
		I	N	I	N	I	N	I	N	I	N
Men	Cancer	7	17	141	67	133	63	96	78	21	24
	Control	17	21	162	80	157	44	74	44	16	7
Women	Cancer	3	3	7	8	7	5	5	3	0	0
	Control	2	10	2	7	6	0	0	0	1	0

(I = Inhaler, N = Non-inhaler)

> which are a reconstruction of the original observations. I have asked for, and have now obtained, confirmation that these are the actual counts originally made. Certain pipe and cigar smokers were originally included on the basis of total tobacco consumed, and I have not been able to secure their removal....

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

"For each of the five tables for men, we may ask how many of the inhalers would have shown cancer, if the proportion had been the same as that among the non-inhalers.

TABLE 2

Cigs. per diem	Expected	Observed	Deficiency
1-4	10.737	7	3.737
5-14	138.380	142	-3.620
15-24	153.095	133	20.095
25-49	109.119	96	13.119
> 49	33.260	21	12.260
Total	444.591	399	45.591

"If, following the method of the Medical Research Council, these differences were ascribed to inhalation as a cause, then inhalers may congratulate themselves on reducing the cancer incidence by over 10 per cent, using a very simple, and even enjoyable method of prevention. This is indeed an underestimate, for pipe smokers seldom inhale, and have a low cancer incidence so that their inclusion has lowered the apparent advantage of inhaling....*

"Should not these workers have let the world know, not only that they had discovered the cause of lung cancer (cigarettes), but also that they had discovered the means of its prevention (inhaling cigarette smoke)? How had the M.R.C. the heart to withhold this information from the thousands who would otherwise die of lung cancer?

"Those who refuse the jump from association to causation in the case of cigarette smoking will not be tempted to take it in the case of inhaling; but the M.R.C. and its Statistical Research Unit think the argument is valid in the first case. Can they refuse to admit it in the second?

"(*Note: Data from which 78 have been removed as they did not smoke cigarettes, but which still include mixed smokers of pipes and cigarettes, give the enhanced effect expected and show apparent protection of about 13 per cent.)"

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

IMPROVED DIAGNOSIS CAUSE OF RISE IN LUNG CANCER RATE

Dr. B. M. FRIED, of the Montefiore Hospital, New York City, makes the following comments in the latest revision of his classical text-book on "Tumors of the Lungs and Mediastinum" (14-f):

> "The tobacco-lung cancer association was also said to be supported by the statistical increase in cases of squamous-cell and undifferentiated-cell types of cancer of the lung. These types were stated to be caused essentially by the tobacco tar. However, the squamous-cell type of cancer is not invariably produced by tar or its derivatives. Thus, the squamous-cell cancer of the lung in the Schneeberg and the Joachimstal miners is induced by radon, and the squamous-cell cancer of the skin, which is induced in man and in lower animals by the use of tar, is also readily induced by the application of other chemical and physical agents....
>
> "It is of interest in this report to note that the incidence of metastases in cancer of the lung has been found to have greatly increased in comparison with the figures reported two or three decades ago. Since squamous-cell cancer is the type of cancer said to metastasize much less vigorously than other types, the incidence of metastases should have declined. There is little doubt that the statistical increase in the squamous-cell type of lung cancer (as in the increased incidence of metastases) is due to improved histological diagnosis and not to the tar contained in cigarettes.
>
> "Adherents of the cigarette-lung cancer association theory state that the rise in the incidence of cancer (which they believe coincided with the increased consumption of cigarettes) started about 3 decades ago and that, at present, cancer of the lungs occurs in about 10 per cent of all cancers. However, almost similar figures were reported by German physicians in the early nineteen-twenties (11-b, 5-j, 15-k, 2-w).... In fact, European physicians of that period had already pointed to the high incidence of pulmonary cancer and focused their attention on the possible reasons for its rise."

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OCCUPATIONAL CARCINOGENESIS

W. C. HUEPER, M.D., Head of the Environmental Cancer Section of the National Cancer Institute, Bethesda, Md., presented a paper on metal cancers of the lung before the Seventh International Cancer Congress in London, England, on July 11, 1959 (37-h):

> "The evidence presented indicates that various metallic carcinogens are capable of producing cancers of the human lung upon proper exposure.
>
> "Information available on the distribution of these carcinogenic metals in the human environment supports the view that metal cancers of the lung are probably much more common than is apparent from published records and may affect not only members of various large occupational groups but also those of the general population.
>
> "Carcinogenic metals and minerals are capable of eliciting carcinomas of different histologic types in the lungs of man and experimental animals. These and other observations cited militate against the claim that cigarette smoking is responsible exclusively or mainly for squamous cell and anaplastic cancers occurring in human lungs.
>
> "The frequent occurrence of squamous cell metaplasias in the bronchial mucosa of man and experimental animals under conditions precluding any significant causal effect of cigarette smoke in the production of such lesions, weakens the etiology specific importance which has been attributed to these changes by supporters of the cigarette theory."

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LUNG CANCER AND TUBERCULOSIS ASSOCIATION

T. W. LEES, M.D., Pathologist of Law Hospital, Carluke, Scotland, in mid-1959 reviewed the statistical data of Doll & Hill, (10-13-d). In his booklet (5-1) he contrasts the "unqualified affirmation" by the British Medical Research Council in 1957 (51-b) that smoking is the major cause of lung cancer, with the fact that no specific cause is known for other common forms of cancer:

> "Cancer of the lung is not only unique in that it is the most rapidly increasing cancer, it is also unique in that it occurs in the same organ as that in which the incidence of acute and chronic disease in youth and middle age has most noticeably decreased in the last fifty years. The most rapidly decreasing common chronic disease--lung tuberculosis--was formerly the commonest single cause of death in middle age. The inverse correlation between the incidence of these two diseases in the last fifty years is far closer than the correlation between lung cancer and cigarette consumption....
>
> "A simple explanation, at least as plausible as smoking and at least part of a general theory, for the increase in lung cancer is that the type of men who would have died forty years ago from pulmonary tubercle in their thirties did not die of this disease twenty years ago and now survive with attenuated or healed tuberculosis to die of lung cancer in their fifties....
>
> "The arguments claiming nearly every type of cancer and disease as due to tobacco smoke are self-refuting. It has been argued that cancer of the bladder (Lilienfeld et al., 1956) (29-1) is associated with smoking, yet the increase in cancer of the bladder in the last fifty years has been small and it is equal in both sexes. Lung tuberculosis (Lowe, 1956) (30-1) is supposed to be precipitated by cigarette smoking, yet this disease has been progressively declining in frequency during the period of increasing cigarette consumption....

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"The Special Case of Lung Cancer.--Lung cancer now tends to occur--it is its recurrent tragedy--in healthy, active, middle-aged men and is not usually associated with previous ill-health. Most other causes of death--hypertension,chronic bronchitis, heart disease, pulmonary tuberculosis, diabetes, many forms of cancer--tend to have a long history of ill-health measured in years. Many of them predominantly affect men over the age of 65.

"Lung cancer is an acute disease. It kills on the average in six to nine months. If one includes cases found accidentally after death or in those which present with multiple metastases the average time is probably less.

"Doll & Hill confirm in doctors the social observation that men smoke progressively less after the age of 55.

"Conclusion.--We conclude that there is a tendency for healthy men to smoke more, and unhealthy men less, than the average; and for healthy men to have a higher and unhealthy men a lower certification of death from lung cancer and other acute disease. It follows that there will necessarily be found a correlation between smoking and lung cancer.

"The evidence for the claim that smoking causes lung cancer is examined.

"1. It is found that the increase in incidence of lung cancer is not paralleled by changes in smoking habits.

"2. The fallacies, difficulties, and limitations of sampling in human studies are discussed.

"3. The general law is stated and developed--that there is a non-causative correlation between the social habits pertaining to good health (such as smoking and drinking alcohol) and the incidence of certified acute disease.

"4. The association of lung cancer and cigarette smoking is a specific example of this law.

"The inference is drawn that there is no good evidence that smoking causes lung cancer."

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THE HIDDEN PART OF THE ICEBERG

Donald MAINLAND, Ch.B., D.Sc., Head of the Department of Statistics at New York University School of Medicine, New York City, in 1957 discussed one of the basic flaws in epidemiologic surveys (12-m):

> "Experimenters' statistics has greatly improved our survey techniques. Thus, the technique of Doll & Hill might fairly be described as not very far from perfect, as a retrospective survey... But all the characteristics, such as sex and age for which allowance was made, are known characteristics, and we can hardly imagine that there are no hidden characteristics, very relevant to the problem.
>
> "In ten years we may know one of these characteristics, and if we make a similar survey then we should not dream of disregarding it, any more than Doll & Hill disregarded sex and age....
>
> "We are far too ready to think that what we see is all that matters; for it is what we do not see that may wreck our conclusions, and we have no radar equipment to detect the underwater part of our iceberg.
>
> "True, for practical purposes we may have to rest content with the results of a survey. For example, smoking is a plausible factor in the etiology of lung cancer, and we may feel impelled to advise people not to smoke; but we should never expect a survey to prove a causal relationship, and we fool ourselves if we think that a probability value, derived from testing survey data, tells us anything whatever about the hidden part of our iceberg."

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III-C 11

LUNG CANCER RISE PARALLELS ADVANCES IN MEDICAL SKILL

John Marshall NEELY, M.D., Assistant Professor of Radiology at the Creighton University School of Medicine, Omaha, wrote editorials in the Nebraska State Medical Journal in April 1954 (2-n) and in July 1959 (3-n) which discuss the difficulty of correct diagnosis of lung cancer:

"The supposed increase in the incidence of primary carcinoma of the lung has attracted so much attention in the press that it seems in order to examine this situation. It is apparent that this seeming increase closely parallels the recent advances in thoracic surgery. Most published dogmatic claims regarding this increase are made on the basis of surgical material. Many of these cases represent the removal of so-called 'coin' lesions from the periphery of the lung. In view of the fact that there is no characteristic clinical, roentgenographic, or histological picture of primary carcinoma of the lung it is doubtful if such a diagnosis is justifiable....

"In earlier publications on this subject, squamous cell carcinoma of the lung was rather uncommon, but present day series nearly all show a preponderance of this histological type. It seems rather obvious that many of these so-called squamous cell carcinomas of the lung are actually metastatic lesions arising from an undiscovered primary focus....

"The question of actual increase of primary carcinoma of the lung was debated as early as 1930. At that time all the autopsy materials from the files of the University of Minnesota were reviewed and no actual increase was demonstrated. It was then the fad to blame the fumes from exhaust pipes of automobiles, rather than cigarettes, for the suspected increase. It seems highly probable that one theory is just about as tenable as the other....

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

"It is felt that the incidence of primary carcinoma of the lung would fall to what has always been considered normal levels if all published data on this type of tumor were limited to autopsied material. It would also help to flatten out the incidence curve if any malignant neoplasm found in the lung would be considered metastatic until proven otherwise by autopsy. At the present time there is no more knowledge concerning the etiology of primary carcinoma of the lung than there is any other type of carcinoma." (2-n)

- - -

"There are very few disease entities of unknown etiology in which cigarette smoking has not been considered the cause. This applies particularly to two various forms of cancer.... Some generations ago cigarette smoking was considered the cause of tuberculosis....

"We have in our files thirteen patients who have been diagnosed as bronchogenic carcinoma of the lung on the basis of lobectomy or pneumonectomy, all of whom at autopsy were found to have primary carcinoma elsewhere with metastasis to the lungs.

"Further food for thought is the fact that primary bronchogenic carcinoma of the lung is twice as frequent in Great Britain as in the United States but cigarette consumption there is half as great as it is here." (3-n)

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

LUNG CANCER RISE PARALLELS INCREASED FACILITIES

R. H. RIGDON, M.D., Professor of Pathology and Head of the Department of Pathology and Laboratory of Experimental Pathology, University of Texas Medical Branch, Galveston, in 1957 discussed the reported rise in lung cancer mortality (10-r):

"Interest in cancer of the lung has increased progressively since 1810.... The question has been asked frequently during the past 50 years -- Is the increase in frequency of lung cancer real or only apparent?

"In 1952, a study was made by Rigdon & Kirchoff (7-r)... (showing) that the reported death rate from cancer of the lung is higher in those States which have a larger number of physicians relative to the size of the population than it is in States which have a relatively smaller number of physicians.

"Likewise, the same death rate is higher in States which have a large number of hospital beds in proportion to the population, than it is in States with a relatively low number of beds....

"Vital statistics are too crude to establish accurately the frequency of cancer of the lung. It is my opinion, based in the available data, that cancer of the lung has not actually increased in proportion to all other neoplasms.

"Tobacco products, especially cigarettes, have been suggested frequently since the beginning of the 20th century as an etiologic agent in cancer of the lungs. The present controversy is only a 'flare-up' of this problem.

"A demonstration of a carcinogen in cigarette tars for the skin of a mouse and a rabbit cannot be accepted scientifically as a carcinogen for the lung of man; such has been known for 25 years or longer.

"The frequency of the habit of smoking by peoples throughout the world during the past several hundred years and the relative infrequency of cancer of the lung should make us critical of the observations suggesting an association between cigarette smoking and cancer of the lung as 'cause and effect.'

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"Diseases other than lung cancer occur in individuals who are heavy smokers without anyone suggesting 'cause and effect.' Furthermore, many individuals have died with cancer of the lung that did not smoke. Scientific studies on this problem should be encouraged because facts may be discovered about the pathogenesis of cancer which may serve as the basis for treatment."

Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

INCREASED INCIDENCE OF LUNG CANCER

Dr. Milton B. ROSENBLATT, Associate Professor of Medicine at New York Medical College and Visiting Physician at the Metropolitan Hospital, New York City, published a book on lung cancer with the collaboration of Dr. J. R. Lisa in 1956 (14-r). In his most recent paper (15-r),he says the universal rise in lung cancer incidence is"more indicative of improved diagnosis and longevity than of increased exposure to alleged carcinogens." He summarized the dissenting opinions on the role of smoking as a cause of lung cancer as follows:

> "1. Cancer of the lung has been an established entity in the medical literature for 150 years, antedating the era of cigarette smoking by a century.
>
> "2. In institutions with routine autopsies and awareness of the disease there has been no real increase in the ratio of lung cancer to total cancers.
>
> "3. The current difficulties in the diagnosis of bronchogenic carcinoma suggest that a percentage of the huge respiratory death rate in the early part of this century may well have been due to lung cancer. If this diagnostic error is estimated as low as 5 per cent, the death rate from lung cancer at the turn of the century would have been as great as it is today.
>
> "4. The validity of the statistical conclusions has been challenged on the basis of improper selection of controls, lack of autopsy confirmation of the cause of death, and lack of correlation between the death rates of the heavy smokers in the survey as compared with the death rates for the total white male population in the United States.
>
> "5. The relationship between induction of skin cancer in susceptible strains of mice and bronchogenic carcinoma remains to be established.... Bronchogenic carcinoma has never been produced in the experimental animal by the use of tobacco or tobacco products."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

THE PROBLEM OF MULTIPLE CAUSATION OF DISEASES

The methodology of investigators of etiologic factors in chronic diseases was examined in 1959 by J. YERUSHALMY, Ph.D., School of Public Health, University of California at Berkeley, and Carroll E. PALMER, M.D., Division of Special Health Services, U.S. Public Health Service, Washington, D.C. (2-y):

> "Much of our knowledge concerning etiologic factors in chronic diseases has been derived from uncontrolled, or poorly controlled, observations.... The major weakness of observations on humans stems from the fact that they often do not possess the characteristic of a group comparability, a basic requirement which in experimentation is accomplished by conscious effort through randomization. The possibility always exists, therefore, that such associations as are observed may, to a greater or lesser degree, be due to factors other than those under study....
>
> "It is, therefore, perhaps not surprising that some data derived from uncontrolled observations are accepted as conclusive by some investigators and rejected by other equally competent observers....
>
> "Whether there are different specific causes for a given chronic disease or a single specific cause involved in different vectors, the practical effects on the conduct of the investigation are the same, namely, that in many of the chronic diseases the investigator is confronted with the problem of 'multiple causation....'
>
> "To use again the example of smoking, even if it were shown to cause lung cancer, the large number of smokers who do not have cancer of the lung testify to the insufficiency of smoking as a cause of the disease, and the existence of lung cancer patients who have never smoked clearly indicates that smoking is not a necessary cause.
>
> "This situation is in contrast to that of diseases where a single specific agent is under suspicion, for in these cases the single agent, although not sufficient for the disease, is nevertheless necessary. Consequently, an essential element in the demonstration of the agent as a cause is that when adequately investigated it can be shown to be present in every case of the disease. Because the characteristics currently under study are neither necessary nor sufficient, investigations of etiologic factors in many chronic diseases lack the advantage of a one-to-one correspondence between cause and effect, in either direction." 2015037955

Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

For further data on difficulties in diagnosing lung cancer see 30-b, 50-b, 32-b, 38-b, 24-c, 38-c, 29-c, 2-f, 3-f, 21-f, 25-g, 5-h, 22-h, 24-h, 53-h, 1-i, 1-j, 7-k, 25-k, 31-l, 28-l, 36-l, 1-m, 2-m, 5-m, 53-m, 24-m, 62-m, 38-m, 11-n, 4-o, 7-o, 8-o, 32-p 45-p, 36-p, 34-p, 23-p, 39-r, 12-r, 23-r, 28-r, 70-s, 53-s, 4-s, 67-s, 64-s, 22-s, 52-s, 41-s, 51-s, 46-s, 47-s, 10-t, 4-u, 5-u, 6-v, 1-w, 31-w 17-w, 1-y

For further reading on inaccurate death recording practices see 5-a, 8-b, 66-b, 28-b, 39-b, 6-e, 5-e, 17-g, 25-h, 43-h, 29-h, 2-j, 3-j, 13-l, 27-l, 6-m, 33-m, 50-m, 38-m, 52-m, 29-p, 30-p, 39-r, 24-r, 53-s, 4-s, 29-s, 11-t, 1-u, 3-u, 4-v, 6-v, 1-w, 18-w, 32-w, 1-z, 2-z, 3-z, 4-z

For further data on bias arising from poor recollection, selectiveness of study groups, and other forms of bias see 7-a, 12-b, 13-b, 14-b, 15-b, 27-c, 14-e, 23-f, 24-f, 22-f, 31-f, 32-f, 19-h, 5-m, 11-m, 44-m, 65-m, 6-n, 7-n, 8-n, 31-p, 25-r, 23-r, 38-r, 70-s, 1-t, 7-t, 10-t

For further data on the effects of improved medical knowledge, facilities and diagnostic practices and equipment see 27-b, 10-c, 7-d, 46-p, 7-r, 8-r, 9-r, 10-r, 13-r, 14-r, 70-s, 17-w, 22-w

For further reading on the effects of survival of increasing numbers of people to older age groups see 11-l, 12-l, 13-l, 6-o, 5-p, 13-r, 14-r, 70-s, 26-s

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For further discussion of the error in applying "cause-and-effect" judgments to statistical associations see 7-a, 12-b, 16-c, 17-d, 14-f, 33-g, 12-m, 25-r, 13-r, 15-r, 17-r, 18-r, 70-s, 1-t

For further data on anomalies and discrepancies in the statistical studies on smoking-lung cancer association see 7-a, 12-b, 13-b, 14-b, 15-b, 72-b, 10-c, 1-f, 2-g, 3-g, 4-g, 12-g, 29-l, 24-l, 7-m, 45-m, 42-m, 6-o, 2-p, 17-r, 18-r, 19-r

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

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IV. WHERE DOES CANCER START IN THE RESPIRATORY TRACT?

There are many histological-pathological considerations that bear on the origins of respiratory cancer. Many researchers are seeking answers to such questions as:

If cancer is caused by inhaled substances, why has there not been a parallel or similar increase in cancer of the mouth and throat as there appears to have been in the lungs?

Why is cancer of the trachea very rare as compared with cancers of the bronchi and lungs?

What are pathologists today finding as to the origins of lung cancers on the basis of cancer cell types?

Do the majority of lung cancers originate mainly in the periphery of the lungs or at divisions of the bronchi and in other parts of the lung reached by inhaled substances?

A number of scientific studies relating to these basic problems have been made and are here grouped under four headings.

A. Oral and Laryngeal Cancer Incidence

B. Studies of the Tracheobronchial Tree

C. Classification of Lung Tumors

D. Site of Origin of Lung Cancer

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

A. Oral and Laryngeal Cancer Incidence

Vital Statistics of the United States for the past twenty years show that the death rate from cancer of the buccal cavity and pharynx has declined from 3.9 (1940) to 3.4 (1957). Cancer of the larynx has fluctuated between 1.1 and 1.3 per 100,000 population during the same years. British mortality from these cancers has paralleled American experience.

A number of American and British writers have discussed oral and laryngeal cancer incidence. Their papers discuss the apparent anomaly between claims that tobacco smoke or other inhaled substances are a cause of cancer in the lungs, whereas there is a lack of increased cancer incidence in oral parts equally exposed. Excerpts from these papers follow:

"If the reported increase in lung cancer is due to tobacco smoke, how does it come about that there is no increase in the incidence of cancer in other parts of the respiratory tract, such as mouth, tongue and pharynx, which suffer a greater exposure to the smoke and for a longer time? In point of fact, there is some slight decrease in these sites."

R. D. PASSEY, 1953 (32-p)

"Cancer of the larynx has not risen as considerably (as lung cancer), although also a mainly masculine disease."

J. S. BOURDIN, 1956 (52-b)

"Despite the fact that the lips and oral mucosa are constantly bathed in the tarry liquor oozing from the tip of the cigarettes and despite the contact of these parts with the smoke coming from the cigarettes, there is no statistical association with cancer of these parts."

W. C. HUEPER, 1954 (34-h; see also 33-h)

"The background of the present paper is the striking difference between the trends of mortality in England and Wales due to cancer of the lung and of the larynx. In contrast to the well-known large increase in deaths ascribed to lung cancer, for cancer of the larynx there has been little change over the past twenty years."

M. P. CURWEN et al., 1954 (23-c)

"It is now certain that cancer of the larynx has not increased in frequency during the very period in which cancer of the bronchi and lungs has become very much more common. It is difficult to understand why this should be so if the inhalation of a carcinogenic substance is a vital factor in producing cancer of the respiratory tract.... Some hidden and hitherto unsuspected factor is responsible for the astonishing increase in 'cancer of the lung.'"

J. MAXWELL, 1955 (46-m; see also 51-m & 45-m)

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

"Although evidence of excessive cigarette smoking frequently is seen in the pharynx and larynx, the rise in incidence of cancer of these structures has not kept pace with that of lung cancer.... Can it be that the relationship between cancer of the lung and cigarette smoking is coincidental?"

M. C. MYERSON, 1955 (41-m; see also 42-m)

"In contrast to the increased incidence of lung cancer, there has been no dramatic rise in incidence in other organs exposed to tobacco smoke. Malignant tumors of the nasopharynx and larynx are of epithelial origin, and if tobacco is a potent carcinogen for the bronchial mucosa it should be equally effective in the upper respiratory epithelium, with which it is in contact in greater concentration. However, no statistical association has been demonstrated between an increased incidence of upper respiratory cancer and increased consumption of cigarettes. The lips and buccal mucosa have also failed to show a significant rise in incidence of malignancy despite the intimate contact with both the smoke and the cigarette tar."

ROSENBLATT & LISA, 1956 (14-r; see also 15-r)

"In 1909, the Registrar-General of the United Kingdom directed attention to the catastrophic increase in males, since 1870, of cancer of the tongue (228%). Contemporary clinical opinion held that unless radical measures to curtail tobacco smoking were enforced, a further increase among males and females could be expected to reach a maximum by 1950 (37-p). Of course, despite increased tobacco consumption, the incidence of tongue cancer is now halved. Today, clinicians are deeply concerned with the avalanche of bronchogenic carcinoma in males and tobacco is again under criticism. Case (30-c) has used cohort analysis to show that in the United Kingdom, coincident with this marked increase in lung cancer, a compensatory fall in several other cancers (especially oropharyngeal) has occurred.....

"It is apparent that experimental and clinical cancer are not identical diseases. The principal divarication between the oncological disciplines pertains to carcinogenesis. The genesis of experimental cancer is mainly exogenous and mutagenic, and a 'cause' is specified. Human cancer, on the other hand, arises in a complex genetic phenomenon and evolves with the ontogeny of the host."

K. W. STARR, 1960 (55-s)

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IV-B

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B. Studies of the Tracheobronchial Tree

Cancer of the trachea is rare, especially for mortality. However, studies of cell changes in the respiratory tract (Auerbach et al., 13-a & 14-a) have shown a higher degree of such changes (hyperplasia and metaplasia) in the trachea than in the lungs and bronchi, although this observation has not been explained. Moreover, the cell changes seem to decline steadily as the examination goes deeper down the bronchi and into the lower segments of the lungs.

Following are selected studies which have produced somewhat different results, accompanied by comments from other authors bearing on the problem. Particular mention should be made of studies of 3000 excised lungs undertaken by 12 eminent pathologists in leading centers throughout the United States.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

DIFFICULTIES IN PATHOLOGICAL INTERPRETATION

Difficulties in making classifications and gradings of cell changes seen under the microscope in studies of slides prepared from sections of tracheal, bronchial and lung tissues have been discussed by Stanley P. REIMANN, M.D., Director Emeritus of the Institute for Cancer Research, Philadelphia, Pa. In a 1960 paper (30-r) he says:

> "Twelve experienced pathologists from various parts of the U.S.A. undertook a study of the pathologic anatomy of the bronchial tree and lungs in specimens obtained from routine autopsy services and surgical excisions. The object was to catalogue changes, sites and incidence in these organs in relation to age, sex, occupation, place of residence and work, use of tobacco, cause of death.
>
> "The classifications used were: normal, hyperplasia, squamous metaplasia, atypical metaplasia, carcinoma in situ, carcinoma. About 3000 cases were investigated yielding 8590 slides from males and 3661 slides from females adjudged suitable. The borderline cases provoked disagreements, many of which could not be reconciled....
>
> "Morphological classification is not a very precise process. The pathologists differed quite steadily and indeterminacy was the rule.... As another 'test,' a number of pathologists reexamined their own slides a year or so later and found they differed almost as much as they differed from one another."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

Tentative conclusions reached in conference by the pathologists were as follows. Dr. Reimann says:

"1. There is no difference in the prevalence of changes, called hyperplasia or metaplasia, at any age above 25 years. Less than 30% of all case studies, including both sexes and all ages, had fifteen sections with apparently normal mucosa.

"2. Males have these changes more often than females, but both metaplasia and hyperplasia do occur frequently in females.

"3. Cigarette smokers in this study have fewer normal sections than non-smokers.

"4. By a rough division of occupations into 'hazardous' (those which may have a high death rate from lung cancer) and those in farming and others, no consistent excess of metaplasia or hyperplasia appeared in any of the three groups.

"5. Study of the occurrence of metaplasia or hyperplasia by the size of the largest city in which the cases have ever resided revealed no differences.

"6. Metaplasia was present in more cases dying from lung cancer than in those which died from other cancers or all other causes of death.

"7. Carcinoma in situ was less and less frequently diagnosed, and then usually only when invasive carcinoma was also present."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

HISTOLOGICAL STUDY DENIES PROGRESSION IN HYPERPLASTIC LUNG CHANGES

Professor G. J. CUNNINGHAM and Dr. D. P. WINSTANLEY, of the Department of Pathology, Royal College of Surgeons of England, also are studying changes in human bronchial epithelium. In a 1959 report (22-c). they say that no abnormal changes were detected in the bronchial lining in nine of the 31 post-mortem lungs studied. One of these was a child of two; four were old women; but four were old men, all of whom had been smokers: One had smoked 20 cigarettes a day up to his death at 80. Of 47 surgical patients whose smoking histories were known, seven had normal bronchial lining, their ages ranging from 49 to 66 years. Three had smoked over 20 cigarettes a day for many years. On the basis of the study, they said:

> "The bronchial epithelium may be perfectly normal in heavy smokers, even in men who have smoked from adolescence and reached a consumption of 40 cigarettes a day....
>
> "Basal cell hyperplasia is a common and conspicuous change. There is often a similarity between the hyperplastic basal cells and the cells of oat cell carcinoma. Whether this is more than a superficial resemblance remains to be proved. We have found nothing to contradict Auerbach's suggestion that a basal cell hyperplasia is connected with cigarette smoking.
>
> "The frequency of squamous metaplasia has long been recognized and our observations have so far provided nothing new.... We have seldom observed changes which could be regarded as intermediate between basal cell hyperplasia and squamous metaplasia, and we have never met with appearances which we interpreted as indicating a transition from one type to the other....

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

"We cannot confirm Auerbach's findings on the frequency of carcinoma-in-situ.... In conclusion, it has become apparent that the responses of bronchial epithelium to noxious stimuli are comparatively restricted and we have reached a stage in the work at which we expect to observe no new histological abnormalities."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

LESIONS THAT MIMIC CANCER

Fred W. STEWART, M.D., Ph.D., Pathologist Emeritus at the Memorial Center for Cancer and Allied Diseases, New York City, in 1959 (41-s) described lesions that are neither cancer nor precancerous, but which closely resemble cancer on microscopic examination. He also described innocent-appearing lesions that do precede cancer, as further evidence of the difficulties encountered by pathologists in diagnosing cancer. As to the lungs, he said:

> "In the lung much interest has of late centered on precancerous lesions because of increasing importance of the cancers. That in situ carcinoma antedates infiltrating cancer is certain if for no other reason than that there is no other way for cancer to begin. As in the uterine cervix, agreement does not exist on where metaplasias, atypias, end and in situ carcinoma begins. There probably is no ascertainable sharp division.
>
> "The same lesions may be found in the trachea where, in view of the fact that tracheal cancer is exceedingly rare, their significance, if such they possess, must be less. The fact that similarly appearing lesions may vary in significance in different sites is not at all unreasonable, nor does it detract from evidence merely because we do not know why such is the case....
>
> "If I can say anything in summary it is that a pathologist can not describe something to the non-experienced individual and leave him with any notion of the groundwork for recognition of the precancerous state. To acquire this information, one must know lesion behavior from personal experience and that of others, and not merely the histologic appearance of tissues and cells. Lesions that even resemble cancer may well not be precancerous. Rather innocent looking processes may, on the other hand, have serious import. One might wax biblical and say 'By their fruits ye shall know them.'"

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

Excerpts from a number of other papers describing the troublesome problems encountered by pathologists in studies of the respiratory tract follow. In a few instances they have been taken out of the authors' general context (25-c, 28-c, 17-c) because of their bearing on the question of cell changes.

"Microscopic changes, which reduce the ability of both the ciliated cells of the trachea and bronchi to rid themselves of possible cancer-causing substances, appear to be traceable to excessive cigarette smoking. However, cancer of the trachea has not increased in parallel with the increase in smoking, as has cancer of the bronchi."

E. V. COWDRY et al., 1957 (25-c)

"A number of investigations have firmly established that the incidence of basal cell hyperplasia, transitional and squamous metaplasia and carcinoma in situ is greater in the tracheobronchial tract of male smokers than in non-smokers. These changes seem to be preceded by an increase in thickness of the epithelium, an increase in size and number of goblet cells and a decrease in the length of cilia. However, it has not been possible from the type of evidence obtained, to decide whether the observed changes in the epithelium represent early stages in the development of bronchogenic carcinoma or whether they are simply non-specific changes associated with the irritatory effects of tobacco smoke and air pollutants.

"Although the incidence of carcinoma of the trachea is low and has shown no rise in recent years comparable to that observed in bronchi, the changes observed in the epithelium of smokers are paralleled by similar changes in the tracheal epithelium. The occurrence of pneumonia leads to epithelial patterns similar to those found in heavy smokers."

E. V. COWDRY et al., 1958 (28-c)

"...A continuation of this study is in progress in order to assemble a sufficient number of results to enable a statistical examination to be made. It is not possible on the type of evidence obtained in the previous study to decide whether the differences represent specific pre-cancerous changes in the epithelium or whether they are simply non-specific changes associated with the chemical irritatory effects of the tobacco smoke.

"For this reason the study has been extended to the trachea and comparisons made between trachea and bronchus in individual cases, since the incidence of carcinoma of the trachea is low and it has shown no rise in recent years comparable to that observed in the bronchi."

E. V. COWDRY et al., 1958 (17-c)

"Recent studies on the occurrence, frequency and distribution of atypical and metastatic local reactions in the tracheal and bronchial mucosa of individuals of all ages and with different disease conditions have not confirmed the much publicized contention of a close and consistent relation of cigarette smoking to these so-called precancerous lesions."

W. C. HUEPER et al., 1960 (44-h)

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

"We do not know if there is any association in this country between cancer of the larynx and smoking.... The study of the etiology of cancer of the lung is complicated by several factors: (1) Cancer of the lung has several different histological forms which may differ in etiology, and these distinctions are lost in figures for total incidence. (2) We do not know which, if any, forms of atmospheric pollution can summate with tobacco smoke as carcinogens.... (3) (Recent studies show) the complex state of our knowledge of initiators and promotors of malignant growth. (4) The significance of carcinoma in situ which, according to Auerbach, occurs on a very large scale, is most difficult to assess, as it is in other forms of cancer (cervix, prostate). (5) Lungs of persons of known smoking history, for chemical and histological research, are difficult to obtain here either from operation or from necropsy."

E. L. KENNAWAY, 1957 (16-k)

"This cytohistological study (of human lungs taken at autopsy or operation) was undertaken in an attempt to clarify the significance of bronchial atypias.... Available evidence does not yet indicate that many of the minor atypias of bronchial cells are either directly related to or prognostically significant in the development of lung cancer. Alterations in ciliated cells and increased numbers of goblet and reserve cells are constant findings in acute and chronic respiratory infections and are seen frequently in sputa of asymptomatic patients.

"Metaplastic transitional cells are seen occasionally in acute respiratory infections and more frequently in chronic inflammatory conditions. They are often difficult to evaluate... but present evidence suggests no particular precancerous potentialities."

D. L. KINSELLA Jr., 1959 (18-k)

"It is of considerable interest that no carcinoma in situ was observed in this study (of 150 lungs removed at autopsy from white male patients without extensive pulmonary diseases). This finding is in contrast to the reported results of Auerbach and associates who observed carcinoma in situ in 35 of 47 patients who smoked more than one package of cigarettes a day."

K. P. KNUDTSON, 1960 (17-k)

"Auerbach.... found carcinoma in situ alongside early invasive carcinoma, and suggested that the former was a stage prior to invasion. These authors point out one contradictory feature of this study in that the above changes were seen as commonly in the trachea as in the bronchi, but it has never been suggested that the incidence of tracheal carcinoma is increasing."

C. L. N. ROBINSON & C. A. JACKSON, 1958 (29-r)

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IV-C 1

C. Classification of Lung Tumors

In recent years pathologists have differed as to whether or not lung cancers are differentiated by any given cell type. Some recent studies which have gone beyond a small circumscribed section of a lesion have shown that many and perhaps most lung cancers contain all the various cell types in varying degrees. This leads directly to the question whether classifications of lung tumors by cell type are valid unless thorough post-mortem studies have been made.

The following excerpts have been provided to illustrate this problem.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

LUNG CANCERS FOUND TO HAVE COMBINATIONS OF CELL TYPES

Francis J. PHILLIPS, M.D., Clair E. BASINGER, M.D., and William E. E. ADAMS, M.D., Department of Surgery, University of Chicago, Ill., reported in 1950 (33-p):

> "The evidence presented in this paper that any combination of cell types may exist in the same tumor belies many of the previous beliefs that a particular cell type has a predilection for some specific area of lung tissue....
>
> "The finding of a greater number of metastases in the peripheral tumors is again an indication of failure of early recognition of the tumor.... The potential malignancy of the so-called adenoma is further substantiated.... The time of diagnosis of the lung tumor appears to be of more prognostic significance than the type of cell found in the tumor or its location in the lung."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

DIFFICULTIES IN CLASSIFYING LUNG CANCERS

The complexity of definition of the various types of lung cancer was the purpose of a special study by J. B. WALTER and D. M. PRYCE (3-w) of the Bland Sutton Institute of Pathology and the Institute for Clinical Research, Middlesex Hospital, London, England, published in 1955. Quotes from their paper follow:

> "At present there is no uniformity in histological nomenclature and the site of origin is a matter of dispute....
>
> "There seems little doubt that the confused histological nomenclature of lung carcinoma is due to difficulties in interpretation of histological appearances rather than any intrinsic complexities in the growths themselves....
>
> "There has never been any difficulty in classifying squamous tumors in which there is no evidence of glandular or oat-celled structure. However, some adenocarcinomata and oat-cell tumors show squamous areas and we should consider that this is merely metaplasia and should not be allowed to confuse the issue....
>
> "Any tumor showing glandular function or structure (including differentiated oat-cell growths) is classified as an adenocarcinoma regardless of any secondary changes.... Similarly any tumor showing oat-celled areas is placed in the oat-cell group, while, if squamous growth only is present, the tumor is classified as squamous-cell carcinoma. Tumors showing neither squamous not glandular differentiation and which were not oat-celled are described as polygonal cell carcinomata.
>
> "No truly 'mixed' growths have been encountered, and it is concluded that the main difficulties in classifying cancer of the lung are due either to secondary changes such as squamous metaplasia or to differentiation in the oat-cell growths."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

IV-C 4

In this paper the authors compare the published classifications of lung cancers by other authors between 1937 and 1953 in two sections: necropsy material, and clinical or surgical material; these show substantial variations in the proportions of the various cell types discussed by these authors, and some other classifications, not only between the post-mortem and resected material, but within these groups. Further, the authors' own series show unexplained differences in classifications between the necropsy and surgical groups:

HISTOLOGICAL CLASSIFICATION OF 207 SURGICAL AND 159 NECROPSY SPECIMENS OF LUNG CANCER

	Surgical series		Necropsy series	
	No. of cases	%	No. of cases	%
Squamous-cell carcinoma	125	60.4	32	20.1
Adenocarcinoma	32	15.5	45	28.3
Oat-cell carcinoma	33	15.9	59	37.1
Polygonal-cell carcinoma	16	7.7	17	10.7
Metastasizing "adenoma"	1	0.5	0	0
Unrecognizable	0	0	6	3.8

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000

IV-C 5

DIAGNOSIS OF PERIPHERAL LUNG TUMORS

Clayton L. N. ROBINSON and Vivian G. PECKAR, of the Thoracic Surgical Unit, St. Charles's Hospital, London, England, in 1956 (28-r) discussed some of the difficulties in locating peripheral lung tumors.

> "A criticism of trying to demonstrate a bronchial origin for peripheral tumors was the feeling that while central or hilar tumors arise in the bronchus -- and the majority were thought to arise in main or lobar bronchi -- peripheral tumors do not. This assumption developed from necropsy studies on advanced lesions. However, Walter & Pryce (37-w) in 207 surgically resected specimens were able to locate definitely the site of origin of growth in 59.4%.... Of the definitely located tumors, 47.1% were central, 3.3% intermediate, and 49.6% peripheral....
>
> "If tumors out of reach of bronchoscopic vision were called peripheral, this group would constitute a great number of these resected. In this respect, a tumor which appears to be a central one in a postero-anterior radiograph is often seen to be peripheral on the lateral film; for example in the apical segment of the lower lobe."

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Source: https://www.industrydocuments.ucsf.edu/docs/pzyk0000